Decision Memo for Outpatient Intravenous Insulin Treatment (Therapy) (CAG-00410N)

Decision Summary

1. The Centers for Medicare and Medicaid Services (CMS) has determined the following.

   The evidence does not support a conclusion that outpatient intravenous insulin therapy improves health outcomes in Medicare beneficiaries. Therefore, CMS has determined that outpatient intravenous insulin therapy is not reasonable and necessary for any indication under section 1862(a)(1)(A) of the Social Security Act. Services comprising an Outpatient Intravenous Insulin Therapy regimen are nationally noncovered under Medicare when furnished pursuant to an outpatient intravenous insulin therapy regimen.

2. Outpatient Intravenous Insulin Therapy (OIVIT) consists of an outpatient regimen of pulsatile or continuous intravenous infusion of insulin via any means, guided by the results of:
   - measurement of respiratory quotient; and/or
   - measurement of urine urea nitrogen (UUN); and/or
   - measurement of arterial, venous or capillary glucose; and/or
   - measurement of potassium concentration;

   performed in scheduled recurring intermittent episodes.

   This regimen is also sometimes termed *Cellular Activation Therapy (CAT), Chronic Intermittent Intravenous Insulin Therapy (CIIIT), Hepatic Activation Therapy (HAT), Intercellular Activation Therapy (iCAT), Metabolic Activation Therapy® (MAT®), Pulsatile Intravenous Insulin Treatment (PIVIT), Pulse Insulin Therapy (PIT)* and *Pulsatile Therapy (PT)*.

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Decision Memo

TO: Administrative File: CAG #00410N
Outpatient Intravenous Insulin Therapy Regimen

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SUBJECT: Coverage Decision Memorandum for Outpatient Intravenous Insulin Therapy Regimen

DATE: December 23, 2009

I. Decision

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II. Background

Terminology

The term outpatient intravenous (IV) insulin therapy (OIVIT) refers to an outpatient regimen that integrates pulsatile or continuous intravenous infusion of insulin via any means, guided by the results of:

- measurement of respiratory quotient; and/or
- measurement of urine urea nitrogen (UUN); and/or
- measurement of arterial, venous or capillary glucose; and/or
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performed in scheduled recurring intermittent episodes.

The term diabetes refers to diabetes mellitus (DM) unless we describe a more specific use. We specify Type 1 or Type 2 DM when the discussion refers to one type rather than to both. The terms hypo- and hyperkalemia refer respectively to abnormally low or high levels of potassium (from the Latin *kallium*) in the blood. The terms hypo- and hyperglycemia refer respectively to abnormally low or high levels of glucose (from the Greek *glykys*) in the blood. The term endogenous is an adjective referring to internal bodily processes or the products of internal bodily processes. Glycogen is a large molecule consisting largely of multiple glucose molecules linked together, and serves as a means to store energy. The term hepatic is an adjective that refers to the liver.

Proteins are comprised of amino acids, many of which are derived from dietary sources. A peptide may be thought of as a small fragment consisting generally of fewer amino acids than a protein. Insulin is an example of a peptide hormone.

A cell may store substances in tiny packets called vesicles, or substances may be dispersed more generally in the intracellular liquid environment (cytosol). Cells release substances through a variety of mechanisms. Small molecules may traverse the cell membrane via specific gates or channels. Cells may also release substances through a process called exocytosis, by which a vesicle will merge with the cell's membrane and discharge its contents directly into the surrounding environment.

Human cells display electrochemical activity to various degrees, depending on their biologic function. The electrical properties of cells are determined by the relative concentrations of electrically charged atoms (ions) inside and outside of the cell. Sodium, potassium, calcium and chloride are examples of ions that play a significant role. When various stimuli cause these ions to move into or out of the cell in a coordinated manner the cell becomes momentarily "depolarized." Energy is required to maintain this electrical balance. Adenosine triphosphate (ATP) is a nucleotide molecule which stores cellular energy in its bonds to its three phosphates; adenosine monophosphate (AMP) and adenosine diphosphate (ADP) store lower amounts of cellular energy with their one and two phosphate units respectively. A kinase is a type of enzyme. Additional terms are defined below as needed.

Scope of this decision
We recognize that various individual components of OIVIT, e.g., insulin, insulin infusion, pump use, metabolic cart measurements, and laboratory testing, may have medical uses in conventional treatment regimens for diabetes and other conditions. We describe many of the more conventional uses of these components in the background sections that follow. In this decision, we are not making (a) coverage determination(s) regarding those other various uses. Coverage for such other uses may be determined by other local or national Medicare determinations and will not be considered here.

We remind the reader that Medicare differentiates the clinical laboratory diagnostic glucose testing performed by medical professionals from the home self-monitoring of glucose that is customarily performed by patients. The test equipment and supplies for home self-monitoring are coverable under the durable medical equipment (DME) benefit and are not payable as diagnostic tests for Medicare purposes. As such, they are not included in the scope of this review.

Commercially available insulin preparations
Various preparations of insulin have FDA approved labeling to improve glycemic control in adults and children with diabetes mellitus. The commercially available insulin products are marketed by many manufacturers. The original animal-derived insulins (beef, pork) have been largely supplanted by recombinant (genetic technology) human insulin or recombinant insulin analogues, [Brogden 1987, Chance 1993, Heller 2007, Hoome 1982, Ladisch 1992] The pharmacokinetic and pharmacodynamic activity profiles of the various insulin products depend on changes in the primary molecular structure of the insulin (native insulin versus insulin analogue), the addition of modifying components such as zinc and protamine, and the route of administration (subcutaneous versus intravenous). [Bruni 1973, Hagedorn 1936, Meneghini 2008, Scott 1935] There are unlabelled uses of IV insulin unrelated to diabetes mellitus, such as the rapid correction of emergent hyperkalemia in the setting of cardiac toxicity. [Allon 1990, Birmbaum in Olson 2004, Hollander-Rodriguez 2006, Kocoglu 2002]

Endogenous insulin

The pancreas is a gland that has both exocrine (digestive enzymes) and endocrine (digestive hormones) functions. The specialized areas producing hormones are islets (of Langerhans) and are scattered throughout the pancreas. The various islets contain "alpha", "beta", "delta", and "epsilon" cells, which secrete the hormones "glucagon", "insulin", "somatostatin", and "ghrelin" respectively. (Andralojc 2008, Dezaki 2006, Docherty 2001, Gromada 2007) Insulin is produced as proinsulin, which is cleaved in the beta cells to produce insulin and C-peptide. C-peptide has no definitively established metabolic effect, but is measurable as a marker for insulin production by the pancreas and to differentiate endogenously produced insulin from administered insulin preparations in blood samples. (Brandenburg 2008, Hills 2008, Norquist 2008)

Insulin and its counter-regulatory hormone, glucagon, are released into the portal vein, through which they enter the liver. The portal venous system is anatomically unique in that venous blood from the small intestine is directed to the liver rather than returning directly through the systemic (general) venous system to the heart. Thus insulin, glucagon, digested nutrients and drugs may be found in higher concentrations in the portal vein than in the systemic venous circulation, and may act upon or be acted upon by the liver before entering the systemic venous circulation. In contrast, digestive enzymes are released into the pancreatic duct and subsequently enter the common bile duct, from which they are delivered into the duodenal part of the small intestine through a natural opening called the ampulla of Vater.

As noted above, insulin has uses beyond diabetes. However, because it is illustrative of insulin's biochemical actions and clinical effects, we have included a detailed discussion of diabetes and insulin below. We recognize that this discussion may be complex for the lay reader, but the underlying topic is itself complex, and we believe that oversimplification will lead to misinterpretation and misunderstanding.

Diabetes

Diabetes encompasses a spectrum of metabolic disorders. Classical Type 1 DM (previously termed Juvenile Diabetes) is an autoimmune disorder in which there is destruction of the pancreatic islet cells that produce insulin, and sometimes also the islet cells that produce counter-regulatory hormones that mitigate hypoglycemia. Because they lack endogenous insulin, Type 1 diabetic patients require insulin replacement in multiple doses throughout the day to prevent ketoacidosis. This contrasts with Type 2 DM (previously termed Adult-Onset Diabetes), in which insulin is still produced, but is secreted in insufficient quantities to meet insulin requirements because of impaired insulin action (resistance). These patients do not require daily insulin to avoid ketoacidosis, but may benefit from insulin supplementation to correct nocturnal hyperglycemia or post-prandial (after eating) hyperglycemia. Patients with mixed disorders may require therapeutic intervention with modalities and regimens from both Type 1 and Type 2 diabetes.

Physiology of insulin secretion

In the following section, we describe the physiology of insulin secretion. We believe this is important because some proponents of OIVIT cite the importance of mimicking the endogenous release of insulin in support of their claims.

Glucose utilization by the body is mediated by both insulin and non-insulin mediated mechanisms (Figure 1). (Baron 1987, 1988, Saltiel, Pessin 2007) The beta cells in the pancreatic islets secrete insulin into the hepatic portal vein (splenic-mesenteric confluence), which drains the mesenteric (largely digestive) organs and supplies the liver. (Bergman 2000, Moore 2003) Insulin levels in the portal vein are substantially higher than in the hepatic vein, which drains the liver, and in other peripheral veins. Exposure to high insulin levels results in suppression of hepatic gluconeogenesis (glucose formation) and an increase in hepatic glycogenesis (glycogen formation). Insulin exposure in the peripheral circulation causes glycogenesis in muscle tissue and triglyceride disposition in adipose (fatty) tissue. (De Meyts 2000)

Figure 1: **Pictorial of Glucose Utilization and the Role of Insulin**

Insulin release is mediated by a variety of activating or inhibitory triggers including nutrients, neurotransmitters, chemical signals and drugs. (Martens 2009, Torres 2009) Glucose enters pancreatic beta cells via glucose transporters (GLUT 2) and is metabolized to ATP. (Ashcroft 1999, 2006, Jensen 2008, Thorens 2001) The relative excess of ATP compared to ADP results in the closure of potassium ATP channels and thus produces cellular membrane depolarization. This depolarization opens voltage-dependent channels and permits extracellular calcium influx. Higher levels of calcium in the cytosol result in insulin exocytosis. (Hou 2009, Weiderkehr 2008)

Insulin release can occur both 1) in response to glucose exposure or mixed meals; and 2) in background oscillation patterns present even during the fasted state. (Goodner 1982, Lefebvre 1987, Porksen 1995, 1997, Weigle 1987) Like other peptide hormones it is secreted in pulses.(Carmel 1976, Dierschke 1970, Goodner 1977, Lang 1979, 1982, Laursen 1995, Stagner 1980, Shapiro 1988, Tannenbaum 1976) Background insulin secretion occurs in high frequency pulses (8-15 minute intervals) and ultradian (recurrent cycles within a 24 hour period) pulses. (Goodner 1977, Lang 1979, Polonsky 1986, 1988, 1998 NEJM), Sturis 1992, Song 2000)

Classically, insulin release was thought to occur in two segments: first-phase, which is a short secretory burst occurring within minutes of a stimulus, and second-phase, which is longer in duration and whose magnitude reflects the extent of stimulus. (Caumo 2004, Cherrington 2002, del Prato 2002. Henquin 2002) First-phase insulin release is diminished in patients with Type 2 diabetes and may be impaired in subjects at risk for the development of Type 1 diabetes. (Cutfield 2004, Fujita 1975, Grendal 2007, Porte 1991, Ratzmann 1981, Smith 1988, Vialettes 1988) As the technologic capability to detect hormone pulsations has improved, it has become apparent that the classic two-phase release reflects an extreme response to a large and sudden glucose load. Under more physiologic stimulus conditions than an intravenous glucose bolus, the occillatory pattern of insulin release changes, but is not as discrete. (Caumo 2004, Lefebvre 1987, Matthews 1991, Polonsky 1995, 1998, Porksen 2002)

Insulin pulsatility can vary by amplitude, inter-pulse interval, and regularity of periodicity. Abnormalities in the background insulin oscillations are present in patients with Type 2 diabetes, in high risk relatives of patients with Type 2 diabetes, and in obese patients with insulin resistance. (Hollingdal 2000, Hunter 1996, Juhl 2001, Lang 1981, O'Rahilly 1988, Radetti 1998, Zarkovic 1999) These abnormal pulsatile patterns can be normalized by weight loss. (Radetti 1998, Zarkovic 2000) Conversely, a pattern of the normal number of pulses, but lower insulin content per pulse, is present in persons engaged in endurance training. (Engdahl 1995) Curiously, although there appears to be a correlation between the insulin pulsatility frequency and peripheral insulin sensitivity, a similar relationship is not present for hepatic insulin sensitivity. (Hunter 1996)

Some investigators have focused on the response of the liver to insulin in the portal venous system. Indeed, it is known that hepatic enzymes involved in glucose metabolism, e.g., hepatic glucokinase (hexokinase IV), phosphofructokinase, and pyruvate kinase require higher insulin levels (200-500 µU/ml) than can be achieved by absorption of subcutaneous insulin into the peripheral venous system. (Aoki 1992, Basu 2000, Clark [Saltiel, Pessin] 2007, Vester 1963) Furthermore, some, but not all, investigators observed increased hepatic extraction of insulin during endogenous insulin pulsations. (Grubert 2005, Meier 2005) It is thought that this entrainment (synchronization) of hepatic insulin receptor turnover optimally suppresses endogenous hepatic glucose output and determines the amount of insulin to be delivered to the peripheral circulation. These findings prompted some researchers to consider insulin treatments which more closely replicate the normal physiologic state and increase the amount of portal vein and hepatic exposure to insulin. Although peritoneal or portal vein delivery could achieve this goal, these routes of administration are very invasive and impractical. Intravenous administration can approximate these levels of hepatic exposure to insulin only if systemic venous insulin levels (and the risks of hypoglycemia) are also high. Nonetheless, some investigators have proposed these alternative routes of insulin administration.

Diabetes and standard insulin therapy

In the following section, we describe the typical route of administration (subcutaneous injection), along with some additional routes of administration that are under development, because all of these are generally self-administered, unlike intravenous insulin. We then describe the typical inpatient settings in which IV insulin infusion might be transiently employed and the types of monitoring that are required for safe administration.

Because insulin and insulin analogues are proteins, they are degraded and/or denatured in the digestive tract. For this reason, the majority of insulin products are given parenterally, i.e. via routes that do not involve the gastrointestinal (GI) tract. The standard outpatient route of administration is a) subcutaneous injection via syringe or pen-cartridge device; or b) subcutaneous infusion from an external pump (usually programmable with bolus and basal rates). (Bohannon 1999, Pickup 1997, Saudek 1997) In patients on peritoneal dialysis, insulin may be added to the dialysate (dialysis fluid). (Chan 1993, Tzamaloukas 1991) Although less invasive methods of insulin administration (inhaled, buccal, or oral) were or are under investigation, patients can safely self-administer insulin via the standard, albeit more invasive, subcutaneous (or intramuscular) injections. (C&E News, DOC, Drugs.com; FDA Dear Doctor Letter, Heller 20007, Khafagy 2007, Royle 2004 with Cochrane update 2008, Yadav 2009)

There are, however, circumstances under which insulin therapy is administered intravenously (IV) by trained medical personnel. Intravenous insulin is used to treat patients with serious or life-threatening metabolic disturbances, e.g., diabetic ketoacidosis and hyperosmolar coma, other conditions limiting the level of consciousness, and/or rapidly fluctuating nutritional needs and intake. (Braithwaite 2003, Furnary 2003, Harrower 1979, Kitabchi 2003, Knapke 1989, Lazar 2000, Malmberg 1997, Park 1992, Pezzarossa 1988, Piters 1977, Pomposelli 1998, Scott 1999, Van den Berghe 2003,Woolfson 1981, Zerr 1997) This route of insulin administration is employed under these types of circumstances because the onset of IV insulin action is rapid and the half-life IV insulin is short; permitting rapid therapeutic intervention in response to rapidly changing clinical conditions. (Turnheim 1988)

When such IV insulin therapy is administered, it is carried out in an inpatient hospital setting such as in the intensive care unit (ICU), the surgical suite, or the step-down unit where the capacity to intensely monitor patients with professional-grade clinical laboratory testing (glucose and electrolytes including potassium levels) and skilled nursing staff are present and enhance safety. (Braithwaite 2004, FDA pump guidance, Grissinger 2003, Hellman 2004, Joint Commission 2000, Paice 1986) The duration of IV insulin therapy is short; patients are switched to sustainable, less invasive, less risky treatment, i.e., insulin injections, other parenteral hypoglycemic drugs, oral hypoglycemic agents, and/or diet, when their condition stabilizes. (Laveria 2008)

When insulin is delivered intravenously, additional precautions are also undertaken during administration because the therapeutic index (the safety margin as expressed by the lethal dose divided by the therapeutic dose) is very narrow when given by this route. (Braithwaite, Grissinger 2003, Hellman 2004) In addition to the potential lethality of hypoglycemia, patients are at risk for hypokalemia because of the intracellular flux (flow from the blood into the cells) of potassium with insulin administration. (Bergman, Rave 1999, Simmons 1994, Tattersall 1999) Hypokalemia itself can be lethal because it precipitates cardiac rhythm disturbances. (Alfronzo, Cohn 2000) Intravenous insulin is administered as part of a diluted solution along with adjunctive potassium. The insulin product typically is diluted to a fixed concentration, e.g., 1 unit insulin/1 cc of normal saline, which is piggy-backed onto the maintenance IV line. (Joint Commission 2000, Novolin insulin label) This IV line flows through an adjustable rate pump for precise dose control. A concomitant IV potassium solution is also piggy-backed into the infusion system. (Novolin insulin label) Doses of insulin, potassium, and hydrating fluids are separately titrated based on frequent results from professional-grade clinical laboratory tests (and not home-use monitoring systems). (Diabetes Today 2009, FDA-Gaines Meter Error, FDA Glucose Meter Alerts, FDA Glucose Meter Advisory Committee Meeting 2001, FDA Meter Review Criteria, Hovorka 2006, Kost 1998, Meguro 2005, Perera 2009) In all cases, the insulin is given as a daily replacement therapy. The doses may be similar to normal physiologic needs or may reflect the increased requirements of insulin resistance. The insulin is not administered intermittently as an adjunctive metabolic stimulant.

Diabetes and metabolic measurements

In the following section, we delineate the typical role of respiratory gas measurements, and the respiratory quotient (RQ) measurement in particular, in medical care and physiologic assessment. We do this because serial outpatient respiratory quotient values are sometimes employed in OIVIT. Metabolism can be determined by measurements of inspired O_2 (oxygen) and expired O_2 and CO_2 (carbon dioxide). (Bartlett 1952, Fuji 2003, Jéquier 1987) The respiratory exchange ratio (RER) (CO_2 elimination/O_2 absorbed across alveolar capillary membranes) is the same as the RQ (CO_2 production/O_2 utilization) under steady state (equilibrium) conditions. The respiratory quotient of completely oxidized substrates is represented by: the number of carbon atoms in the fuel molecule divided by the number of carbon atoms plus the number of hydrogen atoms divided by four and minus the number of oxygen atoms divided by 2. Complete metabolism of pure carbohydrate substrate yields a RQ of 1.0 whereas complete metabolism of fat yields a respiratory quotient of approximately 0.7. The RQ associated with proteins is mid-range and is complicated by a variety of metabolic pathways. In other words, the value of the RQ reflects the extent to which a food substrate is oxidized and the composition of that food substrate. The accuracy and/or utility of this RQ ratio depends on a number of factors including a) the absence of substrate other than carbohydrate, fat and protein, b) substrate disappearance only due to oxidation (and not the urinary losses of glucose or protein that can be present in diabetes), c) the rested state, and d) the fasted state. (Felber 1977, 1980, Golay 2002, Meyer 1980, Schutz 1983) Furthermore, there are errors in the measured metabolic rate that are introduced when the urinary urea nitrogen (UUN) component is not included in the calculation. (Mansell 1990) Typically these measurements are obtained through indirect calorimetry (measurement of heat [energy] using respiratory gases) using metabolic carts (an instrument that measures respiratory gases). Some determinations such as resting energy expenditure (REE) may require the use of additional equations (Fleisch, Harrison-Benedict, or Reed) and patient data. The carts must be regularly calibrated. (Diamond 2007, Hopkins 2003 Policy 159) All devices may not provide comparable data. (Webster 1999, Wells 1998) Typically, RQ measurement is limited to the inpatient setting. Frequently, the measurements are used in the adjustment of nutrition and ventilation parameters. (AARC 2004) Such measurements would not be taken more often than once daily.

There are RQ related measures, Basal Metabolic Rate (BMR) and REE, which are more typically obtained in the outpatient setting. (Compher 2006, Henry 2005) The former is the energy expenditure in the rested, fasted (10-12 hrs), thermally neutral state. The latter does not require the same degree of fasting. BMR (kcal/24 hrs) ~ REE (kcal/24 hrs) = 5.68 VO_2 (ml/min) + 1.59 VCO_2 - 2.17 UUN (g/24 hrs) = 5.46 VO_2 + 1.75 VCO_2. These are used in weight management and weight loss programs. Serial measurements are seldom required. Other measurements, such as VO_2 max, are obtained during exercise for cardiopulmonary or fitness testing. (ATS/ACCP 2003, Diamond 2007, Guimaraes 2008) Multiple determinations within a 24 hour period are seldom required.(ATS/ACCP letter 2009)

By contrast, the advocates of OIVIT interpret the RQ as a measure of carbohydrate metabolic efficacy in diabetic patients and further utilize RQ measurements to assess the response to the insulin infusion and to adjust subsequent insulin infusion doses. (See **OVIT Development** below.)

Outpatient Intravenous Insulin Therapy (OIVIT) Development

OIVIT is a regimen with assorted components which may include insulin, insulin infusion, infusion pump use, metabolic cart measurements, and laboratory testing along with an insulin dosing regimen that is either an explicit algorithm or a more implicit dosing schedule (Figure 2). In OIVIT, insulin is intravenously administered in the outpatient setting to patients to patients who are not critically ill. Most commonly, it is delivered in pulses, but it may be delivered as a drip solution. (ADRI, Diabetes.net, MI, Normedex, Pulse Medix, Strategic Partners-Bionica, VitalCare.) In contrast to conventional therapeutic regimens, the insulin administration is adjunctive to the patient's routine diabetic management regimen (oral agent or insulin-based) or other disease management regimen, typically performed on an intermittent basis (often weekly), typically delivered as a series of fixed duration infusions on a single day, and frequently performed on a perpetual basis without duration limits. (ADRI) Glucose or other carbohydrate is available *ad libitum* (in accordance with patient desire).

Because the insulin infusions reportedly serve, not as hormone replacement therapy, but as a metabolic stimulator, the accompanying metabolic measurements play a somewhat different role in OIVIT therapy. The RQ, which may or may not include a measured UUN component, is claimed to be used as a determination of the patient's carbohydrate oxidative efficacy. In addition, it is claimed to be used to assess the patient's metabolic response to the insulin infusion and to adjust subsequent insulin infusion doses via an explicit or implicit algorithm to achieve an RQ of 0.9 to 1.0. It is not known how adjustments are made for the confounding *ad libitum* (in accordance with patient desire) consumption of glucose or other carbohydrate to reduce hypoglycemia. As many as six serial (pre-, post-) RQ measurements are being obtained during a single treatment session. Blood or serum glucose levels are obtained to reduce the risk of hypoglycemia and/or to adjust subsequent insulin infusion doses via an explicit or implicit algorithm. The precision and accuracy of the methodology used to assess blood/serum glucose levels and the frequency of assessment are not well delineated. (N.B. Personal or home- use glucose monitors do not have the same level of precision as professional point of care diagnostic devices or laboratory chemistry.) (Diabetes Today 2009, FDA-Gaines Meter Error, FDA Glucose Meter Alerts, FDA Glucose Meter Advisory Committee Meeting 2001, FDA Meter Review Criteria, Hovorka 2006Kost 1998, Meguro 2005, Perera 2009) It is not known whether other parameters, e.g., serum triglycerides, and lipid/fat accumulation, are monitored. (See **Insulin Delivery**)(Aguis2009)

Some OIVIT business plans describe/propose the use of closed or semi-closed loop systems for administration in the home setting. (Strategic Partners-Bionica) Blood is to be intermittently aspirated by the infusion pump. Glucose levels are to be detected by sensors and could be monitored remotely. Insulin is to be delivered from commercial cartridges and not via standard diluting solutions. (See FDA Status.)(See NCD Manual 40.3 regarding closed blood glucose control device in the NCD section.)

Claimed benefits for this therapy include 1) improved glycemic control without increased hypoglycemia or with reduced hypoglycemia; 2) improved blood pressure control; 3) decreased progression of nephropathy; 4) reversed autonomic neuropathy (postural hypotension, abnormal diurnal blood pressure, hypoglycemic unawareness); 5) improved wound healing and reduced amputation risk; 6) reduced perception of disability; and 7) improved quality of life. (ADRI, Aoki patent series , Logan-Darroguh 1995) Other claims involve use of the therapy in the peri-islet cell transplant period and use in non-diabetic patients. (Aoki patent series, MI, Mirbolooki 2009, Normedex) Furthermore, it has been claimed that no adverse events have ever been reported for this treatment. (Strategic Partners-Bionica, Normedex)

The physiology underlying this therapy was studied extensively in Europe, but this line of investigation was abandoned there in the early 1990s after a series of conflicting study results. (See Exploratory Studies in Humans.) Of note, respiratory quotients were not used for either dosing or efficacy assessment in the European studies. This is in contrast to their use with the subsequent commercialization of OIVIT in the U.S. (ADRI, MI, Strategic Partners-Bionica, VitalCare, Pulse Medix,Normedex, Diabetes.net, SEC Files) The initial proponents of this therapeutic regimen were Dr. Thomas Aoki and colleagues. To further study the regimen and treat patients, the Aoki Diabetes Treatment Institute (ADRI) was founded in 1986. (ADRI) Dr. Aoki holds patents for metabolic activation therapy for a variety of diabetic and non-diabetic indications. (Aoki patent series) Respiratory quotient measurements are integral to his proprietary treatment regimen, which is available at ADRI and other authorized institutions. (ADRI, ADRI Injunction, MI, Strategic Partners-Bionica, VitalCare, Pulse Medix, Nomedex, CA Cases) A variety of other clinics provide similar therapy. (ADRI, MI, Strategic Partners-Bionica, VitalCare, Pulse Medix, Nomedex, Diabetes.net)

Figure 2: Elements of OIVIT

Analogue = insulin analogue
K = potassium
? = possibly
POC = point of care
RQ = respiratory quotient

OIVIT could involve computer input of data and/or dosing algorithm.

Exploratory animal studies
There have been three important animal studies in which IV insulin therapy was employed. We include them as background as they illustrate the preliminary research in this field. One study was a short-term physiology study. Two studies employed IV insulin as a chronic treatment. In the latter two studies, the IV insulin therapy replaced standard therapy; it was not used as intermittent adjunctive therapy.

Grubert et al. studied 15 fasted non-diabetic mongrel dogs with the 3.5 hour glucose clamp. (Grubert 2005) Endogenous insulin was suppressed with somatostatin. Glucagon was kept constant. Sampling catheters were placed in the portal and hepatic veins as well as the aorta. Infusion catheters were placed in the splenic and jejunal veins (a physiologic location). The dogs underwent three infusion procedures: constant insulin infusion (1 µU/kg/min, pulsatile insulin (12 µU/kg/min over 1 minute every 12 minutes), and pulsatile insulin (3 µU/kg/min over 4 minutes every 12 minutes). The results indicated that hepatic glucose uptake did not differ by the infusion mode or by the amplitude and duration of the insulin pulse when the pulses were given at 12 minute intervals (physiologic for canines).

Weigle et al. studied five streptozoticin-induced diabetic baboons over three approximately month long consecutive treatment periods (pulsatile insulin→ continuous insulin→ pulsatile insulin). (Weigle 1991) Insulin needs throughout the day were determined and then delivered either continuously or as pulses every 10 minutes. (N.B. This differs from the use of intravenous insulin as adjunctive therapy.) Endpoints included four-times daily glucose values, $HbA1_c$, fasting hepatic glucose production (via titrated glucose dilution) and beta-cell function (via response to glucose and arginine loads). Counter-regulatory hormones and other metabolic parameters were also measured. There were no differences by treatment group. Of note, glucagon secretion, which is postulated to contribute to the putative glycemic control associated with pulsatile insulin, was not entrained by insulin. (Matthews 1983, Paolisso 1987, 1988)

Koopmans et al. studied 25 streptozoticin-induced diabetic rats in parallel treatment groups (pulsatile insulin, continuous insulin, control) for approximately 18 days. (Koopmans 1996) Endpoints included fasting glucose levels, fasting insulin levels, diurnal glucose areas-under-the-curve, diurnal insulin areas-under-the-curve and urinary glucose levels. Counter-regulatory hormones, insulin binding, glucose uptake by adipocytes and glycerol production by adipocytes were also measured. Glycemic control was markedly improved as was the anti-lipolytic action of insulin (as measured by glycerol production) in the setting of pulsatile insulin.

Results from animal studies assessing pulsatile IV insulin have been contradictory. The reasons for the disparate animal results are not well understood. The baboons had a higher level of endogenous insulin reserve (comparable to some patients with Type 2 diabetes) whereas the dogs had endogenous insulin suppressed by somatostatin and the rats had a lower insulin level (comparable to Type 1 diabetes). It is possible that higher levels of endogenous insulin obscure small insulin pulses or that longer periods of infusion are required or that the biologic benefit conferred by pulsatility is relatively small in comparison to other environmental factors. (Grubert 2005, Koopmans 1996, Schmitz 1986, 1994, Wiegle 1991)

No animal studies have demonstrated that exogenous IV insulin therapy results in improved glycemic control via activation of hepatic enzymes, e.g., hepatic glucokinase (hexokinase IV), phosphofructokinase, and pyruvate kinase. Hexokinase IV has been studied via glucokinase activators and by genetic over-expression. (Ajius 1995, 2009, Coughlan 2008, Gunn 1973, Hariharan 1997, Mateo 1989, Matschinsky 2006, Pal 2009, Payne 2007, Postic 2001, Soane 1996, Takeuchi 1996, Tilley 2009) In a rodent model using titrated doses of the hexokinase IV gene in a viral vector, even gene activity that was three-times the normal did not result in euglycemia. (O'Doherty 1999) Other studies have suggested that activation of this enzyme could result in hypertriglyeridema and pathologic lipid deposition. (O'Doherty 1999, Pal 2009)

III. History of Medicare Coverage

The outpatient intravenous insulin therapy regimen has several constituent components which are discussed below. We also note other items and services related to other uses of insulin to make clear to the reader that they do not pertain to OIVIT.

A. National Coverage Determinations

There were no prior national coverage determinations on the outpatient intravenous insulin therapy regimen as an integrated program or on its components when furnished pursuant to an outpatient intravenous insulin therapy regimen.

Medicare has a national coverage determination on Glucose Testing as a diagnostic laboratory test, at 190.20 of the NCD Manual. It includes the following among its indications and limitations:

"Blood glucose values are often necessary for the management of patients with diabetes mellitus, where hyperglycemia and hypoglycemia are often present. They are also critical in the determination of control of blood glucose levels in the patient with impaired fasting glucose (FPG 110-125 mg/dL), the patient with insulin resistance syndrome and/or carbohydrate intolerance (excessive rise in glucose following ingestion of glucose or glucose sources of food), in the patient with a hypoglycemia disorder such as nesidioblastosis or insulinoma, and in patients with a catabolic or malnutrition state. In addition to those conditions already listed, glucose testing may be medically necessary in patients with tuberculosis, unexplained chronic or recurrent infections, alcoholism, coronary artery disease (especially in women), or unexplained skin conditions (including pruritis, local skin infections, ulceration and gangrene without an established cause).

Many medical conditions may be a consequence of a sustained elevated or depressed glucose level. These include comas, seizures or epilepsy, confusion, abnormal hunger, abnormal weight loss or gain, and loss of sensation. Evaluation of glucose may also be indicated in patients on medications known to affect carbohydrate metabolism.

Effective January 1, 2005, the Medicare law expanded coverage to diabetic screening services. Some forms of blood glucose testing covered under this national coverage determination may be covered for screening purposes subject to specified frequencies. See 42 CFR 410.18 and section 90, chapter 18, of the Claims Processing Manual, for a full description of this screening benefit."

We note for the reader's convenience the Home Glucose Monitors NCD at 40.2 of the NCD Manual. We are not making a determination on home glucose testing with this decision. Diagnostic testing of glucose levels is distinguished from home glucose testing, which is covered as durable medical equipment (DME).

We note only for the reader's convenience that Medicare has a national coverage determination on Closed-Loop Blood Glucose Control Device (CBGCD) as an inpatient hospital service at 40.3 of the NCD Manual. However, OIVIT as described is not the same as CBGCD. It includes the following indications and limitations:

The closed-loop blood glucose control device (CBGCD) is a hospital bedside device designed for short-term management of patients with insulin dependent diabetes mellitus (Type I). It consists of a rapid on-line glucose analyzer; a computer with a controller for the calculation and control of the infusion of either insulin or dextrose; a multi-channel infusion system; and a printer designed to record continuous glucose values and to provide cumulative totals of the substances infused. Its primary use is for the stabilization of Type I diabetics during periods of stress, such as trauma, labor and delivery, and surgery, when there are wide fluctuations in blood sugar levels. It serves to temporarily correct abnormal blood glucose levels (hyper- or hypo-glycemia) and this correction is made by infusion of either insulin or dextrose. Its use is generally limited to a 24- to 48-hour period because of potential complications; (e.g., sepsis, thromboses, and nonportability, etc.). The CBGCD requires specialized training for use and interpretation of its diagnostic and therapeutic contribution and continuous observation by specially trained medical personnel. Use of the CBGCD is covered for short-term management of insulin dependent diabetics in crisis situations, in a hospital inpatient setting, and only under the direction of specially trained medical personnel.

We also note only for the reader's convenience that Medicare has a national coverage determination on Infusion Pumps at 280.14 of the NCD Manual. However, this addresses the subcutaneous administration of insulin, not the IV administration.

B. Benefit Categories
Because Medicare is a defined benefit program, an item or service must fall within a benefit category as a prerequisite to Medicare coverage: 1812 (Scope of Part A); 1832 (Scope of Part B); 1861(s) (Definition of Medical and Other Health Services); of the Social Security Act.

<u>1. Insulin and Insulin Infusion</u>
Drugs and biologicals and the administration of drugs and biologicals may be considered to be within the benefit category of the Social Security Act section 1861(s)(1), physicians' services; section 1861(s)(2)(A), services and supplies (including drugs and biologicals which are not usually self-administered by the patient) furnished as incident to a physician's professional service; and section 1861(s)(2)(B), hospital services (including drugs and biologicals which are not usually self-administered by the patient) incident to physicians' services rendered to outpatients.

<u>2. Metabolic Cart/Respiratory Quotient</u>
The metabolic testing may be considered a benefit under the benefit category set forth in Title XVIII of the Social Security Act, section 1861(s)(3) (diagnostic tests - other), a Part B benefit.

IV. Timeline of Recent Activities

March 25, 2009: The CMS opened an internally generated National Coverage Analysis (NCA) to evaluate the available evidence for outpatient intravenous insulin treatment, as well as the devices used to administer the therapy and the laboratory monitoring and medical-nursing surveillance required for implementation in the various outpatient settings, and the role for accompanying metabolic testing (including respiratory quotients). The initial 30-day comment period began.

April 24, 2009: The initial 30-day public comment period closed; 187 timely comments were received.

August 31, 2009: CMS met with Dr. Thomas Aoki, Mr. Bruce Parsons and Mr. Dick Costigan from the Aoki Institute.

September 25, 2009: CMS posts the Proposed Decision Memorandum and opens a 30 day public comment period on the proposed decision.

V. Food and Drug Administration (FDA) Status

The outpatient intravenous insulin treatment (OIVIT) regimen under evaluation consists of multiple elements; some of which are intrinsic to the regimen and others which are optional: a biological pharmaceutical agent, an intravenous infusion device, glucose monitoring device, a metabolic cart for the determination of respiratory quotients, and a treatment regimen. The pump may have the capacity to be programmed for the delivery of insulin pulse patterns. The pump may have an integrated glucose monitoring device. The pump may be linked to a computer. A computer may integrate information about glucose levels, prior drug responsiveness, and respiratory quotients as well as other variables. The treatment regimen for OIVIT may be explicitly codified as a treatment algorithm or nomogram or may be more implicit. None of the proposed elements for OIVIT have specifically been approved by the FDA for OIVIT. There are no approved computer systems for the input and integration of glucose and respiratory quotient data for either the determination of an insulin dose or for the determination of an insulin dose linked to a pumping mechanism. The FDA has not approved this treatment regimen as a comprehensive unit.

Although none of the elements used in OIVIT have been specifically approved by the FDA for the OIVIT regimen, regular human insulin, which has long been used off-label for intravenous drips in the in-patient setting, especially intensive care units, did acquire a labeled indication for intravenous use (Novolin R in 2005). On-label use, however, requires adequate monitoring:

INDICATIONS "Novolin R may be administered intravenously under proper medical supervision in a clinical setting for glycemic control";
DOSAGE AND ADMINISTRATION "Intramuscular and intravenous administrations of Novolin R are possible under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia. For intravenous use, Novolin R should be used at concentrations from 0.05 U/ml to 1.0 U/ml in infusion systems with the infusion fluids 0.9% sodium chloride, 5% dextrose, or 10% dextrose with 40 mmol/l potassium chloride using polypropylene infusion bags."

Two insulin analogues insulin, insulin aspart (Novolog) and glusisine (Apidra), which have more rapid onset of action when absorbed through the skin, but not when delivered via intravenous or peritoneal routes, have also acquired FDA approval for the intravenous administration indication. Their labels include similar language regarding the medical supervision, laboratory monitoring, and drug dilution required for safe use.

VI. General Methodological Principles

When making national coverage determinations under section 1862(a)(1)(A) of the Social Security Act, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

For diagnostic testing, CMS generally considers evidence in the hierarchical framework of Fryback and Thornbury (1991) where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information changes the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. Most studies have focused on test characteristics and changes in physician diagnostic thinking and have not considered health outcomes, such as mortality or morbidity. We believe that health outcomes are more important than test characteristics.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

1. Questions

We are providing a summary of the evidence that we considered during our review. This section presents the agency's evaluation of the evidence considered for the assessment questions.

1. *Is the evidence sufficient to conclude that an outpatient intravenous insulin therapy (OIVIT) regimen improves health outcomes in Medicare beneficiaries?*

In order to answer question 1, we asked the following questions about the individual components that comprised OIVIT.

2. *Do outpatient insulin treatment strategies that incorporate diagnostic respiratory quotient (RQ) testing to guide intravenous insulin therapy improve health outcomes compared to strategies that do not use RQ testing?*
3. *Do outpatient insulin treatment strategies that incorporate diagnostic urine urea nitrogen (UUN) testing to guide intravenous insulin therapy improve health outcomes compared to strategies that do not use UUN testing?*
4. *Do outpatient insulin treatment strategies that incorporate diagnostic blood glucose or potassium testing to guide intravenous insulin therapy improve health outcomes compared to strategies that do not use blood glucose or potassium testing?*
5. *If the answer to any of the above questions is affirmative,*
    a. *Which health outcomes of Medicare beneficiaries are improved?*
    b. *What is the duration of therapy required to effect a clinically significant improvement and how durable is that improvement (in the presence or absence of continued therapy)?*
    c. *Which patient characteristics reliably predict a clinically significant favorable or unfavorable health outcome?*

<u>Outcomes of greatest interest</u>

Medicare is most interested in therapeutic modalities that have been shown to improve morbidity and mortality, i.e., hard clinical endpoints, in its beneficiaries. Reliance on intermediate (or surrogate) outcomes, such as change in test results, can be misleadingly encouraging.

For example, early studies in diabetes management led to hypotheses that hyperglycemia itself was the cause of diabetic complications such as neuropathy, retinopathy and macrovascular coronary artery disease. Thus, researchers focused on the improvement of glycemic control as a goal or desired outcome of treatment.

Indeed, the Diabetes Complications and Control Trial (DCCT) demonstrated that glycemic control could blunt the onset/progression of microvascular retinal and renal complications in Type 1 diabetic patients. (DCCT 1993) The United Kingdom Prospective Diabetes Study (UKPDS) suggested the same in Type 2 diabetic patients, but also indicated that the patient management of Type 2 diabetes with its impaired insulin action in combination with other metabolic defects involved more than insulin replacement. (UKPDS 33, 34 1998)

The subsequent studies by the Veterans' Administration (VA) and the National Institutes of Health (NIH) have shown that intensive glycemic control using oral hypoglycemic medications and insulin does not confer major protection against cardiovascular disease and may increase morbidity and mortality. (ACCORD Gerstein 2008, Skyler 2009, VA Abraira 1997, 2003, VA Duckworth 2009) In addition, glycemic control has not been shown to reverse end-stage microvascular diabetic complications in either Type 1 or Type 2 patients and renal disease in Type 2 patients, when its underlying etiology is macrovascular or hypertensive in nature. (Orchard 2006)

Health outcomes of interest include improvements in the following morbidities of diabetes: retinal disease, microvascular renal complications, macrovascular renal disease and cardiovascular disease. Intermediate outcomes such as glycemic control, blood pressure control and blood pressure medication use are not accorded evidentiary weight for the reasons discussed above, as they can be misleading. Treatment burden and adverse effects, particularly severe hypoglycemia and any potential side effects attributable to the metabolic changes induced by the outpatient intravenous regimen of insulin administration such as alterations in serum lipids and lipid deposition in tissue are of interest because of the advanced age and co-morbid conditions present in many Medicare beneficiaries.

Health disparities
The Medicare beneficiary population includes several subgroups of diabetic patients. The largest segment (95+%) comprises older Type 2 diabetic patients (age 65+ years), whose primary cause of death is cardiovascular disease. Minority populations are overly represented in this diabetic population. Younger beneficiaries with Type 2 diabetes frequently have co-morbid conditions, e.g., psychiatric disease, which limit diabetes management. Younger beneficiaries with Type 1 disease are frequently in the Medicare program because they are already disabled by diabetes-related complications. As such, Medicare is interested in treatment modalities that address these complications and clinical conditions. (MCAC 2006)

2. External technology assessments (TAs)

CMS did not commission an external TA for this NCA. We are aware of two external assessments of outpatient intravenous insulin treatment. We describe them below briefly.

1. Blue Cross/Blue Shield-California (BCBS 2001)
The therapeutic regimen was reviewed on February 14, 2001. The following was extracted from the assessment:

"Other alternatives to PIVIT exist for treatment of blood sugar, blood pressure, and kidney disease. Intensive insulin therapy has been documented to produce more sustained effects on glycemic control and antihypertensive therapy (particularly with ACE [angiotensin converting enzyme] inhibitors) to produce excellent control of blood pressure adequate to reduce or prevent progression of diabetic nephropathy. Based on the two randomized, controlled trials, it is difficult to conclude that PIVIT improves net health outcomes as much as or more than the established alternatives. Finally, the substantial drop-out rates in the randomized, controlled trials suggest that maintaining the schedule of weekly PIVIT in addition to daily intensive insulin needed to achieve its potential benefits may be difficult for many patients under conditions of usual medical practice. Therefore, TA criteria 2-5 are not met.

RECOMMENDATION It is recommended that pulsatile intravenous insulin therapy does not meet Blue Shield TA criteria for patients with type 1 diabetes mellitus."

2. Hayes (A proprietary technology assessment and rating firm in Landsdale, PA) (Hayes 2007) This therapeutic regimen was initially reviewed July 14, 2006 and subsequently updated August 15, 2007 and September 29, 2008. The following was extracted from the Executive Summary:
"Important questions regarding CIIIT are:

- *Does CIIIT improve glycemic control and/or reduce incidence or progression of sequelae of diabetes, compared with conventional intensive insulin therapy?*
- *Is CIIIT safe?*
- *Have definitive patient selection criteria for CIIIT been established?"*

"Major complications of CIIIT have not been reported.

Definitive patient selection criteria for CIIIT have not been established.

Conclusions: There is insufficient evidence from the limited number of published studies to conclude that CIIIT is effective in reducing symptoms, improving glycemic control, or preventing diabetic sequelae in patients with type 1 diabetes. Although results of several of the studies suggest that CIIIT may improve glycemic control, facilitate blood pressure control, and/or slow progression of nephropathy, the lack of adequate controls, randomization, and blinding, and the small sample sizes of the available studies preclude definitive conclusions regarding the health benefit of CIIIT. Double-blind RCTs of adequate size are necessary to evaluate this therapy adequately."

3. Internal technology assessment

CMS staff conducted a comprehensive search of materials to address the clinical questions delineated above. CMS staff extensively searched Medline (1965 to present) for primary studies evaluating pulsatile insulin and intravenous insulin therapy. The emphasis was on studies structured to assess long-term efficacy and adverse events. CMS staff likewise searched the Cochrane collection, the National Institute for Health and Clinical Excellence (United Kingdom) appraisals, and the Agency for Healthcare Research and Quality (United States) library for systematic reviews and technology assessments. Systematic reviews were sought to help locate any obscure publications and abstracts.

The CMS reviewed FDA reviews of the registration trials for intravenous insulin, intravenous pumps, glucose testing, and indirect calorimeters as well as FDA safety data for intravenous pumps and insulin. CMS staff reviewed the transcripts from the FDA Advisory Committee meetings on glucose monitoring systems, the warnings on glucose monitoring systems and the guidance document on 510k clearance for external infusion devices. CMS staff reviewed the 2008 NIH/FDA workshop proceedings about closed-loop insulin infusion systems. CMS searched the National Institutes of Health (NIH) Clinical Trials.gov database for ongoing/completed trials of outpatient intravenous insulin therapy. We used internet searches to identify websites with clinical trial results and/or pump information and/or respiratory quotient measurement information, press releases for clinical trials and/or pump information and calorimetry devices and U.S. government regulatory action. Preference was given to English language publications. Keywords used in the searches included: intravenous-insulin, pulsatile-insulin, hepatic activation, metabolic activation, calorimetry, respiratory quotient, metabolic cart, infusion pump and insulin pump.

We reviewed external technology assessments, evidence based guidelines, professional society position statements and public comments. We conducted an internal technology assessment of pertinent animal studies, exploratory physiologic studies in humans and longer-term clinical studies in patients. In addition, we reviewed eight trials listed in ClinicalTrials.gov.

<u>Published Studies: Exploratory Human Physiology Studies</u>

There have been multiple physiologic studies of pulsatile insulin. (See Figure 3 and Table 1) They have been of short-term duration with testing occurring during treatment or immediately after 1-2 days of treatment. Normal subjects, Type 1 diabetic patients, and Type 2 diabetic patients have been tested. Similar to the animal studies discussed in the Background section, these studies used exogenous insulin as replacement for endogenous insulin and not as adjunctive therapy.

Figure 3: Published Human Physiology Studies: Pulsatile Insulin

Table 1: Published Studies of Pulsatile IV Insulin: Exploratory and Physiologic: Human

Study/ Yr Published/ Funding	Endpoints	Patient Type/ Diabetes Type/ Number/ Other Features	Blinding	Randomization	Control	Duration
Related StudiesContinuous Insulin						
Foss 1982 NIH Howard Hughes	Glucose clamp-related parameters Glucose control p glucose & mixed meal loads RQ p glucose & mixed meal loads (not for dosing) → better glucose control	Type 1/non-DM control Poor glycemic control No complications N=5/5 Continuous 72 hr Biostator infusion w less rigid blood glucose parameters than in a euglycemic clamp	No	No	Pre- & post tx Non-DM	4 d
Aoki 1983 NIH	Glucose clamp-related parameters Forearm glucose extraction	Type 1 N=9 Biostator infusion w less rigid blood glucose parameters than in a euglycemic clamp	No	No	Pre- & post tx	4 d

Study/ Yr Published/ Funding	Endpoints	Patient Type/ Diabetes Type/ Number/ Other Features	Blinding	Randomization	Control	Duration
	RQ (not for dosing) → better splanchnic glucose extraction (indirect)					
Positive Results						
Matthews 1983	Insulin binding to monocytes Glucose levels → better glycemic control → more receptor binding	Non-diabetic N=9 (but 3 DCed) Somatostatin suppression of endogenous insulin used; glucagon replaced	No	Random order of tx arms	2 tx arms (continuous vs pulsatile)	2 d
Bratusch-Marrain 1986 Fonds zur Forderung der Wissenschaff-lichen Forschung Osterreichs	Glucose clamp parameters (tritiated glucose) → less HGO for same dose or more suppression w lower doses → suppression more evident with duration of dosing	Type 1 Study A n=8 Study B n=5	No	No	2 tx arms (continuous vs pulsatile P) A= 60% insulin delivery w P B=equal total insulin doses	1 d each infusion

Study/ Yr Published/ Funding	Endpoints	Patient Type/ Diabetes Type/ Number/ Other Features	Blinding	Randomization	Control	Duration
Schmitz 1986 Aarhus University Research Council Institute of Experi-mental Clinical Research Danish Diabetic Association Danish Medical Research Council	Glucose clamp parameters (tritiated glucose) No RQ used → better metabolic clearance, but not lower HGO (perhaps bc of higher insulin doses) & more evident after 3.5 hrs → GH & glucagon same	Non-diabetic N=8 Higher doses of insulin than Paolisso 1991	No	Random order of tx arms	2 tx arms (continuous vs pulsatile)	1 d each infusion (longer 6 hr clamps) Separated by 2-4 wks
Paolisso 1988	Glucose clamp parameters No RQ used → higher glucose infusion rate in the last hour of infusion → improved lipids	Type 2 (no drug) N=8 Somatostatin suppression	No	Random order of tx arms	2 tx arms (continuous vs pulsatile)	I d each infusion

Study/ Yr Published/ Funding	Endpoints	Patient Type/ Diabetes Type/ Number/ Other Features	Blinding	Randomization	Control	Duration
		of endogenous insulin used; glucagon replaced				
Paolisso 1988	Glucose clamp parameters Beta cell response to arginine → more C-peptide suppression in normals → glucagon response to arginine altered w pulsatility	Type 1/non-DM control N=9/7	No	Random order of tx arms	2 pt types Pre- & post tx 2 tx arms (continuous vs pulsatile) Different insulin doses	1 d each infusion
Paolisso 1990	Glucose clamp parameters (tritiated glucose) → higher glucose infusion rate in the last hour of infusion → improved lipids	Non-diabetic elderly N=7 Somatostatin suppression of endogenous insulin used; glucagon replaced	No	Random order of tx arms	2 tx arms (continuous vs pulsatile	1 d each infusion

Study/ Yr Published/ Funding	Endpoints	Patient Type/ Diabetes Type/ Number/ Other Features	Blinding	Randomization	Control	Duration
Ward 1990 National Health & Medical Research Council of Australia Royal Australasian College of Physicians Kellion Diabetes Fdn Novo Labs	Minimal model parameters (tritiated glucose) Insulin binding to monocytes Glucagon & other hormones NEFA No RQ used → more insulin sensitivity → binding reduced → fewer NEFA	Non-diabetic (non-obese) N=8 3 late day meals given	No	No	Pre- & post tx Comparison to prior continuous infusion	1 d
Paolisso 1991	Glucose clamp parameters hepatic glucose output (tritiated glucose)	Non-diabetic (nl wt) N=9 Somatostatin suppression	No	Random order of tx arms	3 tx arms (continuous vs pulses q 13 min vs pulses q 26 min	1 d x3 separated by 1+ wk

Study/ Yr Published/ Funding	Endpoints	Patient Type/ Diabetes Type/ Number/ Other Features	Blinding	Randomization	Control	Duration
	No RQ used → less HGO w q13 min pulse	of endogenous insulin used; glucagon replaced				
Paolisso 1992 Fonds de la Recher-che Scientifique Medical of Belgium Fonds de la Recher-che Facultaire of Liege	Glucose clamp parameters (tritiated glucose) Glucagon → improved metabolism ~ to 33% more continuous infusion insulin	Type 2 Failed oral agents N=7 Somatostatin suppression of endogenous insulin used; glucagon replaced	No	Random order of tx arms	3 tx arms (continuous 88 U/kg vs pulsed 88 U/kg vs pulsed vs 117 U/kg	1 d x3 separated by 5+ d
Schmitz 1994	Glucose clamp parameters (tritiated glucose) Glycerol	Non-diabetic (obese F) N=6 Somatostatin suppression	No	Random order of tx arms	2 tx arms (continuous vs pulsatile)	1 d each infusion (longer 6 hr clamps) Separated by 2-4 wks

Study/ Yr Published/ Funding	Endpoints	Patient Type/ Diabetes Type/ Number/ Other Features	Blinding	Randomization	Control	Duration
	GH & glugcagon	of endogenous insulin used				
	RQ over 30 min- not for tx					
	(urine urea collected for protein oxidation)					
	Tissue NEFA					
	Tissue glycogen synthase					
	Tissue LPL → HGO same → ∑ glucose disposal same → Glycogen synthase same → Suppressed glycerol & lipid oxidation → >LPL → > Glucose oxidation					
Verdin	Glucose clamp parameters glucose infusion rate	Non-diabetic (nl wt)	No	Random order of tx arms	2 tx arms (continuous vs pulsatile)	1 d x2 separated by 1+ wk

Study/ Yr Published/ Funding	Endpoints	Patient Type/ Diabetes Type/ Number/ Other Features	Blinding	Randomization	Control	Duration
1984		N=7				
Fonds National de la Recherche Scientifique	metabolic clearance rate; hepatic glucose output	No somatostatin suppres-sion				
Fonds de la Recher-eche Scientifique Medical of Belgium	(tritiated glucose)	Higher insulin doses than Kerner				
	No RQ used → clamp parameters not different					
Negative Results						
Paolisso	Glucose clamp parameters	Non-diabetic	No	No	2 tx arms (continuous vs pulsatile)	1 d x2
1986	(tritiated glucose)	N=9				separated by 1 wk
	Glucagon levels → glucose turnover not affected	Somatostatin suppression				
		of endogenous insulin used; glucagon replaced				

Study/ Yr Published/ Funding	Endpoints	Patient Type/ Diabetes Type/ Number/ Other Features	Blinding	Randomization	Control	Duration
Paolisso 1987	Glucose levels → Any hypoglycemic effect w pulsatile insulin was most evident at lower glucagon levels	Type 1 N=6 Somatostatin suppression of endogenous insulin used; glucagon replaced at various levels	No	Random order of tx arms	6 tx arms (continuous vs pulsatile + 3 glucagon infusion rates)	1 d x3
Kerner 1988	Glucose clamp parameters → glucose infusion not different	Non-diabetic (nl wt) N=7 Somatostatin suppression of endogenous insulin used		Random order of tx arms	2 tx arms (continuous vs pulsatile)	
Heinemann* 1989 Baxter Travenol	Glucose clamp parameters	Type 1/non-DM control	No	No	Pre- & post tx	1 d x2 w/in 1 wk

Study/ Yr Published/ Funding	Endpoints	Patient Type/ Diabetes Type/ Number/ Other Features	Blinding	Randomization	Control	Duration
	RQ including UUN (not for dosing)	Good glycemic control			2 tx arms (continuous vs pulsatile)	
	Glucose control after SQ insulin during exercise	No complications			Non-DM	
		N=9/3				
	Glucagon level → worse glucose control					
Paolisso	Glucose clamp parameters (tritiated glucose)	Non-diabetic (nl wt)	No	No	4 tx arms	1 d x4
1989	Glucagon	N=6			(insulin contin-uous or pul-satile w gluca-gon continuous or pulsatile)	separated by 1+ wk
Fonds de la Recher-che Scientifique Medical of Belgium	No RQ used → glycemic control not better → endogenous glucose output high & driven by glucagon especially w pulsatile insulin	Somatostatin suppression				
Fonds de la Recher-che Facultaire of Liege		of endogenous insulin used; glucagon replaced				
Italian Government						

Study/ Yr Published/ Funding	Endpoints	Patient Type/ Diabetes Type/ Number/ Other Features	Blinding	Randomization	Control	Duration
Ward	Minimal model parameters	Non-diabetic (non-obese)	No	Random order of tx arms	3 tx arms	Paired infusions on single day
1989	(tritiated glucose)	N=6			(continuous x2 vs pulsatile > continuous vs pulsatile > continuous)	
	Glucagon					
	NEFA					
	No RQ used → suppressed HGO in all → more glucagon suppression → not better glycemic control					

*Aoki was co-author
Levy-Marchal 1983 paper reviewed but excluded because was SQ not IV.
Foss 1993 paper reviewed, but excluded because was SQ not IV.
Pasolisso 1990 reviewed, but excluded because was pulsatile glucagon.

D=Day
DCed=Discontinued
F=Female
GH=Growth Hormone
HGO=Hepatic glucose output
LPL=Lipoprotein lipase
NEFA =Non-esterified fatty acids

Nl=normal
RQ=Respiratory Quotient
Tx=Treatment
Wk=Week
W=With

Published Studies: Longer Clinical Trials
Clinical studies have been conducted by two groups of investigators: Aoki et al. and Dailey et al. (See Figure 4 and Table 2) Weinrauch et al. have studied a subset of the Dailey patient population more extensively. Unlike the physiology studies, these studies used exogenous insulin as replacement for endogenous insulin and not as adjunctive therapy. Non-standard endpoints were used in many of the studies. (Figure 4 and Table 3)

Figure 4: Clinical Studies of Outpatient Intravenous Insulin Therapy (OIVIT)

Table 2: Published Studies of Pulsatile IV Insulin: Extended Use: Human

Study/ Yr Published/ Funding	Endpoints	Patient Type/ Diabetes Type/ Number/ Other Features	Blinding	Randomization	Control	Duration
Aoki 1993 AMSYS	Glucose Control Hypoglycemia	Type 1 N= 20 Refractory Glucose Control Often complications	None	No	Pre-Tx	Not fixed 7 to 71 mo
Aoki 1995A AMSYS B-M Corp	BP Rx Dose	Type1 N= 41 > 32 > 26 (Subset of Aoki 1995C)	Not stated	Yes	X-over	3 mo each arm
Aoki 1995B AMSYS	Orthostatic BP Glucose Control	Type 1 N= 3 Refractory hypotension	Not stated	No	Pre-Tx	3 mo
Aoki 1995C AMSYS B-M Corp	Diurnal BP Glucose Control	Type 1 N= 74	Retrospective	Retrospective Pooled data & selected from reportedly randomized , prospective trials, but all 1º sources cannot be located (See Aoki 1995A)	Yes	3 mo
Aoki 1999 AMSYS B-M Corp	Renal Function Glucose Control	Type 1 N= 31	None	No	Pre-Tx	Not fixed 12 to 84 mo

Study/ Yr Published/ Funding	Endpoints	Patient Type/ Diabetes Type/ Number/ Other Features	Blinding	Randomization	Control	Duration
Dailey 2000 AMSYS	Renal Fxn Glucose Control	Type 1 N= 90→ 71→ 49 Mild to moderate renal dysfunction	None	Initially yes, but duration changed	Yes	Initially 12 mo Later 18 mo
Weinrauch 2007 ADTC Pat Covelli	Glucose Control Renal Function BP & BP Rx Cardiac Mass & Fxn Neuropathy Hemostasis Other Labs	Type 1 N= 18 Mild to moderate renal dysfunction (Subset of Dailey 2000)	Test reader only	Larger group yes, but is subset	Yes	12 mo
Weinrauch 2009 ADTC Pat Covelli	DMIS Survey Renal Fxn	Type 1 N= 19 Mild to moderate renal dysfunction (Subset of Dailey 2000)	Not stated	Larger group yes, but is subset	Yes	12 mo
Weinrauch 2009C ADTC Pat Covelli	Perception of disability with DMIS survey & subsets	Type 1 N= 19 Mild to moderate renal dysfunction (Subset of Dailey 2000)	Not stated	Larger group yes, but is subset and treatment groups pooled for survey analysis	Yes	12 mo
ADTC= Advanced Diabetes Treatment Center B-M Corp= Boehringer Mannheim Corporation BP= blood pressure DIMS= Diabetes Impact Management Scale			Fxn= function Rx= medication Yr= year			

Table 3: Randomized Clinical Studies of outpatient IV Insulin Therapy by Endpoint

Endpoint	Type 1 diabetes	Blind	Glycemic Control	Type 2 diabetes	Blind	Glycemic Control
Glycemic Control	YES (Dailey 2000) HbA1c change in pts w mild to moderate renal dysfunction Change in glycemic control not compared between groups. Appears not to differ. N= 49 (Only 71 of 90 entrants completed 12 mo and only 49 completed 18 mo.) (Intent-to-treat analyses not performed.)	NO	NOT better	NO		
Acute Complications						
Hypoglycemia	NONE			NONE		
Hypoglycemic Awareness	NONE			NONE		
Chronic Complications						
Retinopathy	NONE			NONE		
Nephropathy	YES (Dailey 2000) Creatinine clearance change in pts w mild to moderate dysfunction Change at 12 mo not significant. Change at 18 mo was significant. N= 49 (Only 71 of 90 entrants completed 12 mo and only 49 completed 18 mo.) (Intent-to-treat analyses not performed.)	NO	NOT related to glycemic control	NONE		
Neuropathy-Autonomic	NONE			NONE		
Neuropathy-Sensory	NONE			NONE		
Cardiovascular Disease	NONE			NONE		
Islet Transplant Survival	NONE			Not Applicable		
Other						
Rx Reduction	YES (Aoki 1995A)	NO	NOT better	NONE		

Endpoint	Type 1 diabetes	Blind	Glycemic Control	Type 2 diabetes	Blind	Glycemic Control
	Blood Pressure Rx Dose Change 6 mo cross-over study N= 26 (Only 32 of 41 recruits entered study. Only 26 completed.) (Intent-to-treat analyses not performed.)		NOT related to glycemic control			
Cognition	NONE			NONE		
Other						
QOL	A subset (Weinrauch 2009) of a "randomized' study (Dailey 2000) 12 mo time point data. DIMS survey for disability 24% survey data missing; survey modified N= 19	NO	NOT better NOT related to glycemic control	NONE		
DIMS= Diabetes Impact Management Scale. IV= Intravenous Mo= Month		QOL= Quality of Life Rx= Medication W= With			DC'd= Discontinued	

There have been two semi-independent groups of researchers in this field. We have categorized the studies by research group and subcategorized the studies by topic or design features.

Aoki et al. Studies

Most of the studies conducted by Aoki and colleagues have been case series or retrospective studies without contemporaneous controls. (Tables 1, 2.) (Aoki 1993, 1995b, 1995c, and 1999)

Non-randomized Studies

Glycemic Control/Hypoglycemia

The first study assessed a series of 20 Type 1 diabetic patients with highly variable self-test glucose measurements (undefined) and/or frequent hypoglycemia (undefined). Reportedly, most patients had a chronic diabetic complication. Glycemic control was poor (mean $HbA1_c$ 8.5 %); the mean insulin dose was low (34 units/day) despite attendance at a specialty clinic for one or more years and a four-injection daily insulin regimen. Subjects were followed for 7 to 71 months. Reportedly, glycemic control improved. $HbA1_c$ values from discrete time points, however, were not presented. Rather the change in $HbA1_c$ over time using the method of least squares was employed although there were too few data points to establish linearity for three subjects. Reportedly, glycemic control improved ($HbA1_c$ 7%) without an increase in the daily insulin dose or frequency of hypoglycemia. The authors concluded that *"….the absence of a control group requires that the data presented here be interpreted cautiously"*.

Hypotension

This study was followed by a report of three patients with Type 1 diabetes and refractory orthostatic hypotension (undefined) who were treated with weekly pulsatile insulin for three months. [Aoki 1999c] Patients were assessed with positional blood pressure measurements (regimen defined), ambulatory blood pressure measurements (diurnal time intervals for measurements not defined), tilt table testing, and cardiac autonomic function testing (NDX device from Q Med; paired testing done in two patients), and glycemic control. The orthostatic change appears to be smaller in two subjects; one with modest antecedent and continuing glycemic control ($HbA1_c$ ~ 7.7%) and one with poor control and marked improvement ($HbA1_c$ from 9.5 to 7.5%). The authors suggest that all patients improved and that glycemic control contributed to "*amelioration of autonomic neuropathy*" and high dose insulin may have improved vasoconstriction. The authors report that discontinuation worsened "*postural symptomatology*", but did not provide positional blood pressure readings.

Renal Function

This study was followed by a report of a three-center review of 31 patients with Type 1 diabetes and overt nephropathy (persistent albuminuria > 300 mg/24 hours, but creatinine clearance > 15 ml/min) and treated with four daily injections of insulin. [Aoki 1999] All subjects had received weekly pulsatile insulin for at least one year. Mean values of the changes in $HbA1_c$, creatinine clearance and urinary protein were calculated. Exit endpoint values, and not endpoint values from discrete time points, appear to have been used. No correlative analyses of the change in glycemic control and the change in renal function were presented. Although mean glycemic control improved ($HbA1_c$ 8.6 to 7.6%), mean urinary protein and creatinine clearance did not change. Despite the absence of a control, the authors suggested that "*the minimal decline in creatinine clearance during the observation period clearly indicates that stabilization or arrest of progression of the overt diabetic neuropathy in our study patient cohort*". They further inferred that pulsatile insulin treatment is effective despite treatment duration although they suggested that it might be most effective in the early months of treatment. There was no discussion of whether there was any imbalance in the populations who received treatments for different time periods. There was no discussion of the potential importance of treatment duration as a study variable and how this should be addressed in future studies.

Diurnal Blood Pressure

In a 1995 study by Aoki et al. [Aoki 1995b], the authors state that it is a prospective, randomized three-month trial, which is retrospective only because it was a *post hoc* analysis of patients pooled from multiple studies. Some patients (number unknown) from a randomized trial with two 3-month crossover treatment arms and a total of 26 patients (n= 52 paired treatments). [Aoki 1995a] The source of the remainder of the patients remains unknown. A search of Medline does not reveal the primary publication of any other randomized trials by this author group. The abstract of the 1995b publication suggests that some of the patient data may have been derived from an uncontrolled case series (n= 20) [Aoki 1993], but even this does not account for all participants. [See segment 5 of the 1995c abstract.] Reportedly this study was done to assess diurnal patterns in blood pressure. Insulin doses and blood pressure medications (ACE inhibitors, calcium channel blockers, loop diuretics, and alpha-agonists) and doses were adjusted during the pre-treatment stabilization period and during the treatment period(s).

The methods section does not include any information on blood pressure measurement including types, positions, devices, frequency, and time-frame definition of night-time vs daytime (and whether such definitions were delineated *a priori*). Patients without hypertension (approximately 23%) or normal diurnal blood pressure profiles were not excluded. Patients were not stratified on the basis of potentially important variables such as glycemic control, renal disease severity, presence of hypertension prior to renal disease onset, severity of nocturnal hypertension, and presence of autonomic neuropathy. Only limited mean data results were reported. The authors reported a statistically significant, although biologically small decrease in $HbA1_c$ (0.5%) within the unblinded experimental treatment arm, but did not perform comparative statistics between the two treatment groups. They presented only mean diurnal blood pressure ratios and the temporal changes in the ratios and did not clarify the statistical analyses used on these derived parameters. The use of ratios obscures the primary data and its variability. They did not present the mean diurnal blood pressure measurements and the temporal changes in mean diurnal blood pressure. No correlative analyses between blood pressure change and glycemic control change were presented. The authors concluded that pulsatile insulin treatment prevented further deterioration in the circadian blood pressure pattern and suggested in both this publication and in a 2001 review that the changes were mediated through improvements in autonomic neuropathy. [(Aoki 2001)]

Randomized Studies (Aoki et al.)

Anti-hypertensive Medication Use

The only randomized study of pulsatile insulin by Aoki and colleagues assessed the change in blood pressure medication use after three months in a cross-over study of patients with Type 1 diabetes and hypertension, but with a creatinine clearance > 15 ml/min.[(Aoki 1995a)] Anti-hypertensive medication doses were assigned equivalency units. Patients were not given an absolute hypertensive medication score. Rather, dose requirements "*…were compared to a baseline value and expressed as a percentage change*". Investigators attempted to maintain stable blood pressure values. The authors reported that pulsatile insulin use resulted in a 46% reduction in individual patient anti-hypertensive medication use and suggested that the likelihood of medication discontinuation was greatest in those with the least severe renal disease, fewest baseline medication requirements, and shortest duration of hypertension. The study was not blinded. There were no published power analyses. There were no intent-to-treat analyses. There was notable attrition since only 32 of the 41 enrolled subjects completed the stabilization period (one to three months). Another six were excluded from the per-protocol completer analysis. The mean treatment arm data suggest that during each of the pulsatile insulin phases, the systolic blood pressure readings increased 5 to 10 mm Hg. Assessments of paired t= 0 and t= 3 month treatment arm blood pressure changes for individuals were not presented.

Dailey et al. Studies

The studies conducted by Dailey et al. and Weinrauch et al. are related. (Figure 4, Table 2) The Weinrauch study population(s) are a subset of the Dailey population. (Figure 4, Table 2)

Randomized Studies (Dailey, et al.)

Annualized Creatinine Clearance

The Dailey study recruited Type 1 diabetic patients with creatinine clearances between 30 and 80 ml/min and albuminuria > 100 mg/d. Prior diabetes control with intensive insulin therapy with multiple daily injections and dietary management was not required. Such measures were instituted for patients desiring study entry. The training regimen was in place for a minimum of four weeks, but the time duration was not uniform. No information on the number of entrants to the training regimen was provided.

No information on the prior use of intensive insulin-dietary therapy and the duration of pre-enrollment training and subsequent randomization was presented. Ultimately, 90 subjects from seven centers were enrolled. Presumably the enrollment was 1:1, but this was not stated. Only the treated patients were infused so there was no subject blinding. No null hypothesis was presented (Tables 2 and3). No power analyses were presented. The methods section only briefly described the insulin therapy and referenced the 1993 Aoki paper. Laboratory assessments of glycemic control ($HbA1_c$) and renal dysfunction (serum creatinine, blood urea nitrogen, serum protein, 24-hour protein (albumin), 24-hour urine collection for creatinine clearance) were performed along with blood pressure (systolic-sitting, diastolic-sitting, and mean arterial) and anti-hypertensive medication (% using ACE inhibitors) assessments. Extensive cardiac (left ventricular mass, left ventricular function), autonomic neuropathy (heart rate variation, diurnal blood pressure variation), and hemostatic assessments as well as radionucleotide determination of glomerular filtration rate (GFR), surveys, and other laboratory tests (lipids, advanced glycated end products) were performed at one or more of the centers. (Dailey 2001; Weinrauch 2007, 2009a, 2009b) Seventy-one subjects completed the 12 month study, but it is not known how these subjects were distributed by treatment arm. There was no intent-to-treat analysis. Indeed, there was no complete analysis for those who had completed the 12 month study because the change in an important variable, creatinine clearance, was not statistically significant.

The study was extended for another six months. Forty-nine subjects (54% of enrollees) (experimental treatment arm n= 23; control arm n= 26) completed 18 months of study. Reportedly, the inconvenience of weekly clinic visits was the major reason for drop-out. Again, there was no intent-to-treat analysis. There was an analysis of 18-month completers (Table 4). There was no declared plan with statistical penalties for early/multiple looks at the data and multiple endpoints (Tables 3 and 4). Changes in creatinine clearance were calculated, adjusted to a 12 month basis, and compared to patients in the 12 month cohort, but it is not clear as to whether the 18 month cohort members were included in the 12 month cohort calculations because they were not excluded in the manuscript's Table 1.) The authors report that annualized changes in creatinine clearance were statistically significant (2.21± 1.62 vs 7.79± 1.88 ml/min; p= 0.03) and assert that pulsatile insulin treatment reduces progression of diabetic nephropathy independent of glycemic control, ACE inhibitor treatment or blood pressure control. The values of these variables at entry and exit (18 month), their change and the statistical assessments were not clearly presented. The potential imbalance of glycemic control at baseline (albeit not statistically significant because of small numbers) was not addressed. There were no assessments of respiratory quotient values and treatment efficacy.

Table 4: Variables Important for Outcomes in Completers of 18 Months of Dailey Study

Study Variables	Control t=0 mo	Control t=18 mo	Experimental t=0 mo	Experimental t=18 mo
HbA1c (%)	9.13	8.19	8.61	7.68

Systolic Blood Pressure (mm Hg)	133.0	-	133.6	-
Diastolic Blood Pressure (mm Hg)	79.2	-	76.9	-
Mean Arterial Blood Pressure (mm Hg)	97.1	98.6	96.7	95.3
ACE Inhibitors (% patients)	77 (Unclear if entry or exit)	-	70 (Unclear if entry or exit)	-
Other Antihypertensive Agents (% patients)	-	-	-	-
Serum Creatinine (mg/dl)	1.66	-	1.50	-
24-hour Creatinine Clearance (ml/min)	59.6	-	55.3	-
24-hour Urine Protein (mg/d)	2107	2609	2057	2362
24-hour Urine Albumin (mg/d)	-	-	-	-

Weinrauch et al. Studies
The Weinrauch populations appear to constitute a subset of the Dailey population.

Glycemic Control/Creatinine Clearance/Echocardiographic Findings

In the earliest study (2007) there were 18 patients whereas in the latter of the studies (2009a & b) there were 19 patients. This discrepancy was unexplained. Unlike the study above, analyses were conducted after 12 months of treatment. In the 2007 study of the role cardiovascular mechanisms might play in renal disease progression of pulsatile insulin treated diabetic patients, the blind was limited to only readers of study tests. No null hypothesis was presented (Tables 2 and 3). No power analyses were presented. There was no declared plan with statistical penalties for multiple endpoints. The analyses appear to be limited to those who completed the 12 month study and not to all entrants, i.e., intent-to-treat. There appears to be a problem with patient number accounting. In the experimental treatment group, 17% of patients were reported to have edema. This would not be possible with the n= 10 denominator. Echocardiographic measurements and functional assessments, autonomic function, and hemostatic laboratories were not thought to have changed during the study or to differ between treatment arms. However, there appears to be baseline imbalance or a trend to baseline imbalance in mean arterial pressure (MAP), an important variable in a study assessing the role of OIVIT and cardiovascular factors on renal dysfunction. Control 103.8±3.4 vs. experimental 96.2±2.7mmHg. [Weinrauch 2007] . This imbalance favors the OIVIT intervention arm. There was a similar imbalance for glycemic control.

Glycemic control improved for the study population as a whole. Indeed glycemic control may have been better and improved more in the control arm although statistical significance may have not been reached because of small sample size: Control t_0= 9.8± 0.5% and $t_{12\ mo}$= 8.0± 0.3%; Experimental t_0= 9.1± 0.6% and $t_{12\ mo}$= 8.5± 0.6%. Absolute creatinine clearance and the change in creatinine clearance reportedly did not differ by treatment group: Control t_0= 55.4± 7.0 ml/min and $t_{12\ mo}$= 45.8± 7.0 ml/min; Experimental t_0= 58.4± 7.0 ml/min and $t_{12\ mo}$= 55.4± 8.7 ml/min. Statistical significance may not have been reached because of small sample size, but even if the values were statistically significant, their biological significance and whether they can be extrapolated over time is uncertain. No correlation calculations between changes in glycemic control and changes in renal function with corrections for baseline renal function and baseline glycemic control were presented. No correlation calculations between renal function and carbohydrate oxidation were presented. Reportedly, RQ values increased immediately after infusions 0.854 to 9.54 in the initial weeks vs 0.826 to 0.915. There was no explanation as to why the baseline level relative carbohydrate oxidation appears to have decreased over the course of treatment and why the response to treatment appears to have declined over the course of therapy. Despite these findings and questions, the authors assert that pulsatile insulin with its improved fuel efficiency is responsible for preservation of renal function.

Author Modified Self-report Disability Survey

In subsequent analyses, the authors used the Hammond-Aoki Diabetes Impact Management Scale (DIMS) (44 self-report questions-six point scale) to assess its relationship with renal function and glycemic control [Hammond 1992; Weinrauch 2009a] and to measure perceived disability [Weinrauch 2009b] although it is not clear that the treatment contributed to better renal function as measured by creatinine clearance or improved glycemic control as measured by $HbA1_c$. The authors did not comment on the validity of using quality-of-life testing in groups in which the treatment was not blinded. The authors did not indicate whether such a survey was validated for longitudinal data or only cross-sectional data. [Watkins 2004] The authors acknowledged that up to 24% of survey response data could be missing for individual respondents. They addressed this by data interpolation; mean treatment group data for a question was substituted for the respective missing data. It is not clear as to whether data were excluded because intent-to-treat analyses were not performed. The authors did not present the comparative results of the DIMS for the treatment groups (baseline values, exit values, 12 month exit values, change in values [12 month completers], change in values [intent-to-treat]). The authors did report that longitudinal changes in DIMS (if any) did not correspond to changes in renal function or glycemic control.

The investigators reformatted that data and conducted additional analyses. They analyzed each survey question for statistically significant change and then excluded questions in which no longitudinal change was found. They reclassified the remaining questions into "emotional" and "physical" responses (Table 5). They determined that the five "physical" questions indicated neurologic status. They then compared scores of the 12 question DIMS subset, the seven question "emotional", and the five question "physical" subset with various study parameters. They reported that "*changes in the five physical questions... correlated with stable creatinine, stable creatinine clearance, and decrease in left ventricular hypertrophy*" although there appears to have been post hoc determination of the renal function and left ventricular mass categories and patients were pooled regardless of treatment status—suggesting that the study was more an assessment of the abbreviated/subcategorized DIMS test than of the therapeutic intervention. [Weinrauch 2009a] Nonetheless, they also reported that "*pulsatile intravenous insulin, when added to standard multiple-dose insulin therapy, was demonstrated to improve subjective perception of neurologic disability…*" on the basis of the unblinded testing results of the five question "physical" subset. [Weinrauch 2009b] Although such survey data are typically interpreted and validated as a unit, the authors did not provide validation for these changes. Nor did they provide substantiation (by physical exam or other testing) for the "physical" questions. There was no declared plan with statistical penalties for multiple endpoints. Neither study clarified a role for respiratory quotient testing.

Table 5: Selected Subset of the Hammond-Aoki Diabetes Impact Management Scale

Author Categorization of Questions	Question
	During the past month:
Emotional	How much time were you lacking enough energy?
	How well have you slept?
	How often have you been able to function well in your usual occupation?
	Have you participated in and enjoyed family life?

Author Categorization of Questions	Question
	Have you eaten what you wanted to?
	Have you felt depressed?
	Have you felt optimistic about your diabetes?
Physical	Have you been bothered by blurring of vision?
	Did burning, tingling, pain, or numbness bother you in your hands?
	Have you been bothered by feeling faint/dizzy on sitting/standing up?
	How often did you have diarrhea?
	How often were you able to function sexually as well as you wanted?

<u>Other Studies</u>

We did not find published studies on the utility of pulsatile insulin in wound healing and amputation risk reduction.

We did not find published studies of pulsatile insulin in the peri-whole pancreas transplant or peri-islet transplant period despite published speculation about its utility. (Mirabolooki 2009)

4. Medicare Evidence Development and Coverage Advisory Committee (MEDCAC)

A MEDCAC meeting was not convened for this issue.

5. Evidence Based Guidelines

Numerous agencies and professional groups (Agency for Healthcare Research and Quality [AHRQ], American Association of Clinical Endocrinologists [AACE], American Association for Respiratory Care [AARC], American College of Cardiology [ACC], American College of Chest Physicians [ACCP], American College of Physicians [ACP], American Diabetes Association [ADA], American Dietetic Association [ADA], American Geriatrics Society [AGS], American Heart Association [AHA], American Thoracic Society [ATP], Canadian Diabetes Association [CDA], Endocrine Society, Juvenile Diabetes Research Foundation [JDRF], Scottish Intercollegiate Guidelines Network [SIGN], and Veterans Health Administration [VHA]) were queried about guidelines regarding intravenous insulin therapy and metabolic cart measurements. Many of these groups have a variety of guidelines for diabetes, nutrition, and cardiopulmonary disease management.

We found no evidence-based guidelines addressing the use of outpatient intravenous insulin therapy, the use of calorimetry to direct dosing or monitor intravenous insulin therapy in any type of patient, and/or the use of calorimetry in diabetic patients. Only the CDA addressed intravenous insulin and did so in the "In-hospital" chapter. ***"Role of Intravenous Insulin Infusion.*** *Intravenous (IV) insulin infusion therapy should be considered during critical illness, or other illness requiring prompt glycemic control, or prolonged fasting (NPO status) (7). IV insulin infusion therapy should be administered only where frequent blood glucose (BG) monitoring and close nursing supervision are possible. Staff education is a critical component of the implementation of an IV insulin infusion protocol. IV insulin protocols should take into account the current and previous BG levels (and, therefore, the rate of change), and the patient's usual insulin dose."*

6. Professional Society Position Statements

American Association of Clinical Endocrinologists (AACE)
We received the following statement from the American Association of Clinical Endocrinologists (AACE).

In 2004, an AACE task force addressed this issue and submitted a report to the AACE Board of Directors which essentially determined, after an extensive review of available data, that no definitive long-term benefit from intermittent intravenous insulin therapy could be identified. The AACE Board of Directors approved the Task Force's report and, since that time, has not seen any study or other evidence that would cause the Association to readdress the issue.

American Diabetes Association (ADA)
The ADA issues positions statements, expert committee reports, workgroup reports, technical reviews, and consensus statements. Upon review, none of these documents address outpatient intravenous insulin, whether pulsatile or not. None of these documents address the use of calorimetry and respiratory quotients in managing diabetic patients.

a. Position Statements (http://care.diabetesjournals.org/content/32/Supplement_1/S98.full.pdf+html; Accessed 6/15/09)
b. Committee Reports and Consensus Statements (http://care.diabetesjournals.org/content/32/Supplement_1/S96.full.pdf+html; Accessed 6/15/09)
c. Technical Reviews (http://care.diabetesjournals.org/content/32/Supplement_1/S95.full.pdf+html; Accessed 6/15/09)
d. ADA Diabetes Care: Insulin Administration ADA Position Statement Diabetes Care, Vol 27, Suppl 1, Jan 2004: S106-S-109. (http://care.diabetesjournals.org/content/27/suppl_1/s106.full.pdf+html; Accessed 6/15/09)
e. Nutrition Recommendations and Interventions for Diabetes: A Position Statement of the ADA (http://care.diabetesjournals.org/content/31/Supplement_1/S61.full.pdf+html; Accessed 6/15/09)

Several years ago, the ADA was asked to assess the pulsatile insulin therapeutic program. The presented data were found not to be persuasive. (Communication with Richard Kahn, Ph.D., Scientific Director; September 2009)

Endocrine Society
Since the publication of the proposed decision, the Endocrine Society has adopted a position supporting noncoverage of OIVIT. See Vigersky letter [PDF, 75KB].

Department of Defense
There are no centrally determined positions on insulin therapy. Pulsatile insulin therapy does not appear to have any/any significant use in the Army (Dr. Robert Vigersky; Walter Reed; personal communication March 2009) or the Navy (Dr. Patrick Clyde; National Naval Medical Center-Bethesda; personal communication March 2009)

Indian Health Service
Outpatient insulin therapy does not appear to have any/any significant use in the Indian Health Service (Dr. Susan Karol, chief medical officer for the IHS; personal communication August 2009)

Veterans' Health Systems
There are no centrally determined positions on insulin therapy. Pulsatile insulin therapy does not appear to have any /any significant use in the VA system (Dr. Leonard Pogach, Director-VA New Jersey Healthcare System, Center for Healthcare Knowledge Management; personal communication March 2009)

7. Expert Opinion

We received the following from David M. Harlan, M.D., Chief, Diabetes Branch, National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health

At Dr. Koller's request, I have reviewed the claims pertaining to pulsatile intravenous insulin delivery's ability to reverse diabetes complications, or to improve clinical islet transplantation outcomes, whether that pulsatile insulin is delivered in the peri-operative period, in the post surgical period, or for rescue therapy. I am unaware of any data I consider scientifically credible to justify those claims.

Please feel free to contact me should you have questions.

See full text at http://www.cms.hhs.gov/determinationprocess/downloads/id231Harlan.pdf [PDF, 32KB].

8. Public Comments

Public Comment Period: March 25, 2009 – April 24, 2009

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. The CMS uses the initial public comments to inform its proposed decision. The CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

During this initial public comment period, the CMS received a total of 187 comments from individuals/groups. The majority (n= 134) were patient testimonials about their own outpatient intravenous insulin treatment; three were testimonials in support of family members who had received outpatient intravenous insulin therapy. The remaining comments came from non-physician health care professionals (n= 21), physician clinicians (n= 17), academic physicians (n= 2); an attorney (n= 1), a health insurance industry representative (n= 1), and assorted or unspecified contributors. The majority favored CMS coverage of outpatient intravenous insulin therapy; five did not; two provided non-specific comments. Six provided literature citations and/or other materials with their comments but no new scientific publications were uncovered. Full text comments without personal health information can be viewed at: http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=231.

Public Comment Period on the Proposed Decision: September 25, 2009 – October 25, 2009

During this public comment period, the CMS received a total of seven public comments. Five of these individuals commented during the first comment period, but made more extensive remarks during the second comment period. One comment came from a health care provider and developer of pulsatile insulin in the U.S., a second came from a laboratory and business affiliate of the developer, a third came from a technology investor, a fourth came from a clinical investigator-author, the fifth came from an officer in a diabetes organization, and the sixth and seventh came from unaffiliated persons. Five favored immediate coverage, one explained his study and favored further research, and the last commented on health care reform.

No new clinical studies were provided. Several tangential references without complete citations were recommended for review. Several commenters discussed judicial decisions regarding coverage in California.

We note that CMS was not a party to the State court decisions cited by commenters, nor is the Agency bound by those decisions. We also note that such materials do not constitute scientific evidence upon which we rely when making national coverage determinations.

Because of the length of the commentary by several of the commenters, the comments have been tabulated by topic below. Full text comments without personal health information may be viewed at: www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=231.

Commenter	Comments	CMS Response
	Scope of OIVIT	
Aoki *Author *Inventor & patent holder of treatment algorithms	*Raised objections to including insulin infusion regimens other than the patented Aoki MAT treatment in the NCD review and analysis.	*Multiple variations of intravenous insulin infused in the outpatient setting were considered and included under the CMS designated class name OIVIT. *CMS did review the patents and patent applications for MAT-type therapy and MAT-type infusion pumps to better determine the scope of the proprietary treatment(s).

Commenter	Comments	CMS Response
	Scope of OIVIT	
*Consultant to Aoki Diabetes Research Institute (ADRI) * 1st period comments too * Favored coverage		*In its review, CMS did distinguish between pulsatile and continuous infusion, the characteristics of the pulses, and other ancillary aspects of treatment.
Arcangeli *Co-author *Lab research associate *Business associate in Metabolic Industries, Inc. * 1st period comments too	*Stated that the MAT is not a broad class of therapies, but is a single therapy with multiple names.	*Multiple variations of intravenous insulin infused in the outpatient setting were included under the CMS designated class name OIVIT. The therapies were reviewed as a class and as discrete entities.

Commenter	Comments	CMS Response
	Scope of OIVIT	
*Favored coverage		
Parsons *International Technology Ventures *1st period comments too *Favored Coverage	*Stated that it was a gross simplification to consider MAT within OIVIT.	*See above response.
Aoki	*Stated that he did not use glucose clamps in MAT and that discussion of studies that employed insulin infusion as part of a glucose clamp are not germane.	*Animal and human physiologic and short-term clinical studies of insulin infusion, especially those of pulsed insulin infusion were reviewed for completeness. Specific animal studies were recommended by Goodner and Polonsky. *The glycemic clamp technique provides a relatively high degree of precision about the insulin infusion and the subsequent glucose utilization by target tissues and any glucose production by the liver.
Arcangeli	*Stated that a euglycemic clamp study does not resemble MAT therapy.	*See above response.

Commenter	Comments	CMS Response
	Scope of OIVIT	
		*The clamp technique is used to maintain a relatively constant glucose level. This would be important when comparing the efficacy of various insulin infusions (including dose, continuous vs pulsatile, and pulse characteristics). The Biostator was one of the devices used for clamps. This closed-loop system also could be used for insulin infusions in clinical and research settings where the precision of the glucose level could vary more, e.g, where the goal is hypoglycemia avoidance. *In a "Restoration of Glucose Homeostasis in Insulin-dependent Diabetic Subjects: An Inducible Process", Foss, Vlachokosta, Cunningham, and Aoki in 1982 state "The artificial β-cell unit (Life Science Unit, Miles Laboratory, Inc, Elkhart, Indiana)" "(known as the Biostator and no longer commercially available)" " used in this investigation is composed of a blood withdrawal system coupled to a fixed matrix glucose oxidase-glucose sensor that continuously monitors the blood glucose level. On the basis of this glucose level or the rate of change of the blood glucose concentration, the infusion system delivers insulin or glucose into a peripheral vein to achieve a pre-determined glucose level. This device is capable of returning relatively uncontrolled insulin-dependent patients to the euglycemic state in 2-3 hours and maintaining pre- and postprandial blood glucose levels in the normal range (70-150 mg/dl) for as long as seven days." Of note, the insulin infusions in this study were not noted to be pulsatile. *References for clamps are included in the CMS bibliography. Of particular note is the reference "Development of the Biostator Glucose Clamping Algorithm" by Clemens et al. 1982. "Infusion is activated to maintain a patient's blood glucose concentration within a selected range."
Arcangeli	*Stated that the animal studies are not germane.	*Animal and human physiologic and short-term clinical studies of insulin infusion, especially those of pulsed insulin infusion were reviewed for completeness. As stated in the NCA review, the results were contradictory. Animal studies may provide important guidance for subsequent human clinical studies. See comments by Goodner and Polonsky.
Parsons	*Stated that the animal studies are not germane.	*See above response.
Aoki		

Commenter	Comments	CMS Response
	Scope of OIVIT	
	*Stated that only ADRI and Metabolic Industries have licenses for his therapy and that other entities have been ordered to "cease and desist". Stated that CMS identified non-licensed entities as licensees.	*CMS delineated a variety of groups that offered this class of therapy. CMS noted that franchise-type arrangements exist. CMS does not verify licensing agreements. The information in the cited parentheses reflects reference documents in the bibliography.
Arcangeli	*Stated that MAT is a patented treatment- available only at licensed centers. Other entities have been ordered to "cease and desist", and the SEC has been notified. NCA referenced websites have disappeared.	*CMS has retained hardcopies of referenced website material.
Parsons	*Stated that only ADRI and Metabolic Industries have licenses for this therapy	*See response to Aoki comments above.
	Disease Background	
Parsons	*Stated that 445,000 are disabled by diabetes and that MAT would prevent problems and save money.	*No further references were provided.
Scott	*Stated that diabetes is a chronic disease which affects millions of patients via a myriad of physical systems and that MAT would prevent problems and save money.	*No further references were provided.

Commenter	Comments	CMS Response
	Scope of OIVIT	
*Diabetes organization not found with web search *1st period comments too *Favored coverage		
	Treatment Background	
Arcangeli	*Stated that RQ measurements are used to determine insulin doses, but that no computer inputs or algorithms are used. *Later stated that "CIIIT uses a complicated therapy algorithm involving high doses of insulin and should never be casually imitated. Providers and staff must complete a training course…."	*These discrepancies in the description of MAT therapy have not been reconciled. The patent descriptions provide no further illumination. *See comments by Goodner, Heinemann, and Millis.
Arcangeli	*Stated that the inclusion of papers on the various routes of insulin administration may have impaired the analysis of OIVIT.	*Information on the various routes of insulin administration was included in the background section because insulin is typically self-administered except in the hospital setting.
Arcangeli		*CMS understands that the MAT subset of OIVIT is provided as adjuvant therapy and is dosed episodically.

Commenter	Comments	CMS Response
	Scope of OIVIT	
	*Stated that MAT is not an alternative therapy; it is an adjunctive therapy for refractory or problematic patients. *Stated that the pharmacologic effects of MAT differ from those of SQ insulin.	*CMS understands the differences in the pharmacokinetic/ pharma-codynamic profiles of insulin given by different routes. * The NCD non-covers all out-patient intravenous insulin administration.
	FDA	
Aoki	*Stated that other companies have made questionable claims including FDA approval of therapy.	*The FDA has not approved or cleared OIVIT treatment regimen(s) or specific devices for OIVIT treatment regimen(s).
	Nature of therapy	
Aoki	*Stated that MAT therapy is not directed at glycemic control, but rather is directed at the provision of insulin to target tissues to improve metabolism and thus reduce complications.	*Regardless of the stated etiology of an intervention, blinded, randomized, outcome studies with hard clinical endpoints are necessary to establish efficacy. One of the benefits of MAT therapy listed on the website www.adri.org/faqs.html#1 , however, is "improved blood glucose control'. *See comments by Lachin.
Arcangeli	*Quoted the NCA on the limitations of glycemic control in the prevention of cardiovascular disease and macrovascular or hypertensive renal disease and the reversal of microvascular complications.	*These limitations were well delineated in the CMS MEDCAC in the Summer of 2006. Investigators were encouraged to consider other etiologic pathways. *Regardless of the stated etiology of an intervention, blinded, randomized, outcome studies with hard clinical endpoints are necessary to establish efficacy.

Commenter	Comments	CMS Response
	Scope of OIVIT	
		* See comments by Goodner, Heinemann, Lachin, and Polonsky.
Arcangeli	*Stated that genetic over-expression of hepatic enzymes in glucose control (hexokinase IV, phosphofructokinase, and pyruvate kinase) was not germane. *Stated that the Torres 2009 reference is incorrect.	*This enzymatic pathway is the one addressed in the "Sleeping Liver" by Aoki. Investigators have explored induction of these pathways by pharmaceutical agents and gene expression. The results have not been uniformly successful, e.g., sometimes very high levels of over-expression are required. This pathway may have significance, but solid clinical data delineating the means for safely and effectively activating this pathway have yet to be demonstrated. Indeed Felber et al. in a series of articles in the 1970s and 1980s in which RQs are employed postulate that glycogen storage may be more important than oxidation in some forms of diabetes and obesity. *The correct citation was O'Doherty 1999 and not Torres 2009.
Parsons	*Stated that large bolus doses of insulin mimic the action of the normal pancreas and enhance the effect on tissues and that Dr. Aoki had invented a way to achieve this without simultaneously inducing hypoglycemia. *Stated that MAT improved glycemic control, but also appeared to have effects on diabetic complications which were not related to glycemic control. Stated that this was the reason that CMS rejected the results of the Dailey study. *Stated that clinical outcomes are more important than etiology.	*Regardless of the stated etiology of an intervention, blinded, randomized, outcome studies with hard clinical endpoints are necessary to establish efficacy. An estimated annualized rate of glomerular function decline is not a hard clinical endpoint. In addition, the primary endpoint did not reach statistical significance after 12 months. Drop-out was high prior to 12 months and prior to the *post hoc* observation interval of 18 months. This limits generalizability of any results. Furthermore, there was no adjustment for sequential statistical testing. Any statistical significance would be diminished. See comments by Hayward and Lachin. *Did not reconcile the results between the Aoki 1999 paper in which decreased renal function decline was attributed, in part, to improved glycemic control and the Dailey paper in which glycemic control was non-contributory.

Commenter	Comments	CMS Response
	Scope of OIVIT	
	Metabolic assessments	
Aoki	*Discussed how RQ measurements assess hepatic glucose oxidation. *Reported that infection or pain could alter RQ response to MAT treatment.	*No human clinical data to support claims were provided. *The RQ data from Foss, Vlachokosta, Cunningham, and Aoki "Restoration of Glucose Homeostasis in Insulin-dependent Diabetic Subjects: An Inducible Process" (1982) were obtained from 5 normal and 5 type 1 diabetic subjects using a Biostator and continuous insulin infusions. *Felber et al. in a series of publications in the 1970s and 1980s in which RQs were employed observed different degrees of carbohydrate oxidation in type 1 and type 2 diabetes patients. *See comments by Goodner, Heinemann, and Millis.
Arcangeli	*Stated that RQ measurements are used to determine insulin doses, but that no computer inputs or algorithms are used.	*No further treatment information was provided.
Parsons	*Stated that RQ levels assess therapeutic efficacy and have been essential for obtaining clinical data for published papers.	*No further validation data were provided.
Aoki		

Commenter	Comments	CMS Response
	Scope of OIVIT	
	*Stated that inclusion of urinary nitrogen measurements is not required. Cited early physiologic work by Foss. (Specific citation data not provided.)	*RQ measurements are gross assessments of metabolism. They are most reliable when conducted in a steady-state condition, e.g., the fasted state and immobile state, and when all components of nutrition are included. No subsequent urinary nitrogen data from clinical trials was provided. See comments by Goodner, Heinemann, and Millis. See editorial by Heinemann 2001.
Arcangeli	*Stated that urea nitrogen measurements are not usually obtained.	*CMS presumes that this refers to urinary urea nitrogen levels, which may be obtained as part of comprehensive RQ assessments * No further references were provided.
Aoki	*Stated that although potassium levels may decrease with insulin infusions, this phenomenon occurs only with longer infusions. ADRI does monitor potassium levels in patients with borderline low levels.	*No human clinical data to support claims were provided.
Arcangeli	*Stated that potassium is not routinely monitored in MAT.	*See insulin drug labels for IV administration.
Aoki	*Stated that hypoglycemia (< 50 mg/dl) occurred in < 1% of ADRI treatment sessions.	*Hypoglycemia is a well established complication of IV insulin even in a highly monitored in-patient setting. The commenter did not provide information that reconciled expected hypoglycemia rates and reported clinic rates. Monitoring procedures and glucose rescue rates were not provided.
Parsons		*See above response.

Commenter	Comments	CMS Response
	Scope of OIVIT	
	*Stated that hypoglycemia (<50 mg/dl) occurred in < 1% of ADRI treatment sessions (unpublished data). Encouraged CMS to visit ADRI.	
Arcangeli	*Stated that there have been no reported cases of hypertriglyceridemia or pathologic lipid deposition with MAT.	*Concerns about hypertriglyceridemia and abnormal lipid deposition have been raised for pharmaceutical agents which activate enzyme pathways for hepatic glucose. These putative adverse events are targets for rigorous safety monitoring. Because these pathways are the same as/overlap with those activated by MAT, systematic collection of such data in OIVIT is warranted. *No human clinical data to support claims were provided.
Arcangeli	*Stated that adverse events did not occur because the procedure mimics nature and monitoring was done.	*No information on monitoring procedures was provided.
	Evidence Base	
Aoki	*Stated that "…where no effective therapy is available, new therapies that show improvement, even in a small number of patients, are usually called 'promising' rather than 'no evidence of benefit'.	*The metabolic pathway this therapeutic modality purports to activate may play a role in diabetes/diabetes complication management. Indeed, pharmaceutical agents that alter these enzyme pathways for hepatic glucose are under development. The data generated thus far as well as any that might be generated by the ADTC studies, however, while sufficient for hypothesis generation, are not/will not be definitive . *See comments by Hayward, Heinemann, Lachin and Polonsky. See ClinicalTrails.gov. See ADTC Research Compendia.
Arcangeli		*CMS uses the principle of evidence-based medicine in its decisions. These principles are outlined in the methods section and the accompanying appendix.

Commenter	Comments	CMS Response
	Scope of OIVIT	
	*Stated that the current evidence base was sufficient to support coverage of CIIIT brittle diabetes, hypoglycemic unawareness, excess hypoglycemic with intensive therapy, refractory hypertension, refractory orthostatic hypotension, and diabetic nephropathy. *Stated that they would be willing to present observational data for other indications.	*See Mulrow 2001. See Duke University Medical Center Library "Evidence -based Clinical Practice Resources" at the following website www.mclibrary.duke.edu/subject/ebm/ebmpyramid.html.
Arcangeli	*Repeatedly referred to the MPCQT reviewer in its comments. Challenged the 2001 Blue Shield technology assessment and stated that the incidence of diabetic renal failure would not be so high if the alternatives delineated in the technology assessment were effective. *Stated that Blue Shield had a conflict of interest because of the financial implications of the court rulings.	*The acronym MPCQT referred to the Blue Shield Medical Policy Committee on Quality and Technology. The comments appear to have been taken from ADRI commentary on the 2001 Blue Shield technology assessment. *CMS conducted an independent review of an updated database. CMS includes descriptions of all available technology assessment in its NCD document.
Arcangeli		*CMS conducted an independent review of an updated database. CMS included descriptions of all available technology assessment in its NCDs. The Hayes group was contacted directly because it is a proprietary assessment group. The letter ratings are not for public release.

Commenter	Comments	CMS Response
	Scope of OIVIT	
	*Commented that the Hayes technology assessment concluded that the treatment had potential, but unproven benefit (vs the lowest rating no proven benefit and/or not safe). For this reason, CMS should provide coverage and help design future studies.	
Arcangeli	*Stated that the Aoki 1993 study in 20 "brittle" patients constituted a controlled study because the degree of glycemic control improvement was similar to or superior to that in the DCCT with one-third of the expected hypoglycemic events,	*The Aoki 1993 paper described a small case series with an extrapolated historical control, not a separate contemporaneous population. Variables which could have contributed to the claimed improvement in hypoglycemic awareness/decreased hypoglycemic event rate, e.g., increased patient support vs the pulsatile insulin, were not delineated.
Arcangeli	*Stated that the Aoki 1995 study in 3 patients with refractory postural hypotension constituted a controlled prospective study. *Stated that these results had been replicated in a larger patient group.	*The Aoki 1995 paper described a case series with a pre-post sequential self-control design. *No publication for the replicate study was provided
Arcangeli	*Stated that the Aoki 1995 study of circadian blood pressure changes is significant because it showed improved glucose control and biological change which will result in decreased end-organ damage.	

Commenter	Comments	CMS Response
	Scope of OIVIT	
	*Noted that CMS would have like to have known about hypoglycemic events, and stated that "This is both the joy and grief of researching CIIIT-we cannot afford to measure and report the entire list of parameters that CIIIT affects in other systems…".	*The Aoki 1995 paper described a *post hoc* analysis of a patient population not otherwise described in the published literature. The ambulatory blood pressure readings may be significant, but describe a surrogate endpoint. The relationship between glucose control, which improved by 0.5 $HbA1_c$ unit % and blood pressure control was not assessed. Given the potential relationship between renal dysfunction and blood pressure and the disparate relationship between glycemic control and renal function decline in the Aoki 1999 and Dailey papers, it would have been important to conduct such analyses. Given that altered circadian blood pressure and hypoglycemia, especially hypoglycemic awareness, may be reflections of autonomic neuropathy, having such data from the apparently largest MAT study would have been useful for assessing risk:benefit albeit limited to persons with Type 1 diabetes.
Arcangeli	*Discussed the Aoki 1995 cross-over study in patients with Type 1 diabetes. *Stated that there was no significant drop-out. *Stated that the drop-out rate during the run-in has no impact on interpretation of the data. *Stated that glycemic control was not contributory to the lowered anti-hypertensive medication requirements in this. *Stated that CMS discussion of proteinuria was irrelevant.	*Limited conclusions can be drawn from small studies with large drop-out-whether within the run-in period or the actual treatment period. Nine subjects of 41 dropped out during the run-in period and another 6 were excluded from the treatment period analyses. Furthermore, study design depends on maintaing blood pressure at steady state. There were small increases in systolic blood pressure. *Proteinuria was not discussed for this study by CMS.

Commenter	Comments	CMS Response
	Scope of OIVIT	
Arcangeli	*Stated that CMS erroneously focused on the lack of changes in proteinuria and any effects from increased monitoring and treatment feedback in this long-term nephropathy case series study by Aoki 1999.	*Limited conclusions can be drawn from uncontrolled case series data with variable observation periods. *Glycemic control was reportedly improved by 1.0 $HbA1_c$ unit % in these patients and renal function decline blunted. No correlative analyses for these two outcomes were conducted. *CMS stated that "Although mean glycemic control improved"…, " mean urinary protein and creatinine clearance did not change". In the absence of a control population and variable observation periods, *CMS does not concur that the lack of change in these parameters clearly demonstrated that renal function decline was blunted in response to OIVIT. *The commenter did not reconcile the disparate etiology between the Aoki 1999 paper in which decreased renal function decline in an uncontrolled patient population was attributed, in part, to improved glycemic control and the Dailey paper in which glycemic control was non-contributory.
Arcangeli	*Discussed the Dailey paper. *Stated that there was no significant drop-out and that the primary reason for drop-out at the time of study extension was "the time required for weekly clinic visits". Indicated that Dailey drop-out rate was not unexpected and cited Lewis 1993 3 year study (26%) and Mogensen 1995 2 year study (26%).	*The primary endpoint was annualized creatinine clearance at 12 months. Ninety subjects enrolled; 71 completed 12 month; 49 completed 18 months. The drop-out rate, the failure to correct for multiple observations, the use of a surrogate endpoint, and the study of Type 1 diabetic patients limits assessment of efficacy and generalizability to the Medicare population. See comments by Hayward and Lachin. *CMS could not locate the statement attributed to it in the proposed document "..the absence of a reduction in urinary protein in both groups was also unexpected". *CMS discussed the DCCT in the context of the available knowledge base.

Commenter	Comments	CMS Response
	Scope of OIVIT	
	*Stated that because an intent-to-treat analysis was not performed, any discussion of such an analytic deficiency by CMS because the results might be positive. *Stated that CMS wrote that "the absence of reduction in urinary protein was unexpected". *Stated that CMS discussion of anti-hypertensive therapy and dietary protein restriction was superfluous. *Stated that any discussion of the DCCT was not-relevant because patients with overt nephropathy, such as those in the Dailey study, were excluded from the DCCT.	
Arcangeli	*Stated that CMS "also speculates that it would take years of CIIIT to prevent progression of end-stage renal disease" while also having stated that the current Dailey and Aoki studies suggest that" CIIT can stave off renal failure for years".	*CMS noted the need for long-term clinical trials with hard endpoints and the limitations of surrogate endpoints. * See comments by Hayward, Lachin, and Polonsky.
Parsons	*Discussed both the Aoki 1999 and Dailey papers.	*See above response sections.

Commenter	Comments	CMS Response
	Scope of OIVIT	
Parsons	*Stated that "…CMS has steadfastly refused to consider anecdotal evidence of long term use of the technology in 38 patients over an average of more than 13 years….". Stated that CMS did not consider the long-term results on these 38 patients which were presented to the Agency at a meeting because they were not peer -reviewed and published. *Stated that CMS does not give credence to testimonials in public comments whereas the judge in the CalPERS case did.	*CMS uses the principle of evidence-based medicine in its decisions. These principles are outlined in the methods section and the accompanying appendix. See Mulrow 2001. See Duke University Medical Center Library "Evidence-based Clinical Practice Resources" at the following website www.mclibrary.duke.edu/subject/ebm/ebmpyramid.html.
Parsons	*Stated that there are areas where Dr. Aoki and CMS could co-operate to develop conclusive trials. *Stated that this "is precisely the kind of technology envisioned when the Medical Clinical Trials program was established by Congress". *Stated that effectiveness could be shown via (a) demonstration project(s) in Medicare and/or Indian Health populations.	*The Coverage with Evidence Development program may provide coverage for items/devices/services under select criteria at the discretion of CMS. *There is no statutory Medical Clinical Trials program. President Clinton issued an executive order to encourage enrollment of Medicare beneficiaries in clinical trials. Routine costs may be covered for appropriate deemed clinical trials. *CMS (ORDI) may also conduct/arrange for demonstration projects regarding coverage based on statutory decree and funding or internal decision. *See comments by Lachin, and Puklin.

Commenter	Comments	CMS Response
	Scope of OIVIT	
		*See section for Professional Societies regarding the IHS.
Parsons	*Stated that, in the setting of underpowered studies, CMS has not established that the treatment does not work and so should provide coverage.	*The evidence presented is insufficient to conclude that OIVIT is, as set in statute, "reasonable and necessary" for any treatment.
Parsons	*Stated that treatment should be provided on a compassionate use basis.	*CMS uses the principle of evidence-based medicine in its decisions.
Scott	*Stated that many reputable organizations had published studies and would not have done so if there were reservations. *Stated that there was no evidence that MAT did not improve health outcomes. *Stated that double-blinding would be unethical.	*No additional published studies were provided. *See comments by Heinemann, Lachin, and Polonsky.
Scott	*Stated that patient/provider testimonials were significant evidence and were not given sufficient consideration by CMS.	*CMS uses the principle of evidence-based medicine in its decisions. *See prior CMS comments.

Commenter	Comments	CMS Response
	Scope of OIVIT	
Weinrauch *Author *1st period comments too *Favors more research	*Discussed the Dailey and derivative Weinrauch studies. *Discussed an abstract presented at the ADA 2009. *Stated that additional studies in select populations is warranted, but that feasibility and funding issues resulted in discontinuation of the technique at his institution (Harvard-Joslin) in the 1990s and that determination of benefit with hard endpoints for diabetic complications is prohibitively expensive for the private sector. *Stated that additional studies, without blinding, are warranted.	*The 2009 ADA abstract was not provided. *Prospective, randomized, blinded controlled studies provide the best data -especially when compliance or efficacy might be affected by differential provider input/support. *See comments by Heinemann, Lachin, and Polonsky.
	Experts	
Aoki	*Stated that experts in OIVIT therapy should be consulted and that the field is small because funding and research has been directed at glycemic control.	CMS reasonably accords greater evidentiary weight to independent expert opinion from persons who do not have personal interests in the matter under consideration.
Parsons		In the proposed decision memorandum we stated that we expected "to received expert opinion on the proposed decision". We would reasonably expect to receive such opinion after the publication of the proposed decision itself.

Commenter	Comments	CMS Response
	Scope of OIVIT	
	*Stated that CMS had not yet obtained expert opinions on OIVIT ,and MAT prior to publishing the proposed decisions, but would be doing so.	CMS makes its coverage decisions on the basis of available scientific data. More evidentiary weight is given to more rigorous data.
Parsons	* "Without such firsthand visits" [with patients and doctors] "CMS will continue to 'hide behind' the pontification of 'experts in the field' with no actual experience using the technology….".	
	Other	
Aoki	*Quoted the California state administrative law judge "The Blue Shield of California's Medical Policy on Quality and Technology is not enforceable in this action. The policy was not enacted until February 2001, almost three years after the denial actions that compose this action,….." .	*The comments do not challenge the Blue Shield technology assessment. Rather they appear to challenge the use of a negative technology review and assessment to deny insurance claims for MAT. A formal Blue Shield policy on MAT was developed after some claims had been paid.
Aoki	*Stated that CMS should review the CalPERS decision about coverage.	*CMS previously reviewed the CalPERS decision and has included it in the NCD bibliography. CMS bases its decision on its review of the scientific literature.
Arcangeli	*Stated that the critique of the Blue Shield technology assessment has been rebutted (in court) and CMS has failed to address this in the proposed NCA document. Stated that he would repost.	*CMS previously reviewed the Blue Shield technology assessment, the CalPERS decision, and the Blue Shield decision. All are included it in the NCD bibliography. CMS bases its decision on its review of the scientific literature.

Commenter	Comments	CMS Response
	Scope of OIVIT	
Parsons	*Stated that "outstanding results" " swayed the courts of California to conclude that Metabolic Activation Therapy is both safe and effective". Stated that "CMS has made no mention of these court decisions even though evidence of the proceedings was presented to CMS." *Stated that the CMS decision further increased the dichotomy between the court mandated coverage in California and the lack of coverage by insurance carriers.	*See above response.
Scott	*Stated that Blue Shield was sued over coverage and ordered to pay for coverage. *Stated that the fiduciary agents for CalPERS were sued over coverage, and that an administrative law judge determined that MAT was not an investigational therapy. *Stated that CMS should have considered the court cases in the NCD.	* See above response.
Parsons		

Commenter	Comments	CMS Response
	Scope of OIVIT	
	Stated that CMS stated in a recent meeting that potential savings to Medicare are not of interest to CMS.	*The comment appears to be based on a misunderstanding of the statement that is routinely delivered to those developers of drugs, devices, and services who make presentations to the Coverage and Analysis Division (CAG) in CMS. CAG prepares NCDs on the basis of scientific data to determine that coverage which is "reasonable and necessary" for Medicare beneficiaries. It does not perform cost analyses. It does not prepare comparative effectiveness studies. It does not prepare cost effectiveness studies. It does not establish reimbursement levels.
Parsons	*Discussed the start-up costs for clinics. Believes that operating costs will come down in an analogues fashion to hemodialysis clinics. Noted that no formal cost-benefit analyses have been conducted.	*CMS makes its coverage decisions on the basis of available scientific data.
Unspecified *Healthcare reform issues	*Expressed concern about health care reform and loss of care for senior citizens	*CMS makes its coverage decisions on the basis of available scientific data.
	Testimonial	
Arcangeli	*Started that patients in the studies experienced improved physical outcomes and quality of life and that this is why they continued treatment at an off-campus site.	*No additional published studies were provided.
Patient	*Reported improvement in glycemic control and neuropathy	*No additional published studies were provided.

Commenter	Comments	CMS Response
	Scope of OIVIT	
* Favored coverage		

VIII. Analysis

Introduction
National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act. §1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See §1862(a)(1)(A) of the Act.

The Medicare regulations at 42 CFR 410.32(a) state in part, "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem." Thus we look for evidence demonstrating how the treating physician uses the result of a test, such as the respiratory quotient (RQ), for the management of a patient with diabetes who is undergoing intravenous insulin treatment and whether insulin treatment strategies that incorporate diagnostic respiratory quotient testing to guide insulin therapy improve health outcomes compared to strategies without RQ testing. This section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment.

This section presents the agency's evaluation of the evidence considered and the conclusions which were reached.

Discussion

Outpatient intravenous insulin therapy (OIVIT) encompasses a large array of treatment regimens with associated services and testing. The various individual components of OIVIT, e.g., insulin, insulin infusion, pump use, metabolic cart measurements, and laboratory testing, may have medical uses in conventional treatment regimens for diabetes and other conditions. We described many of the more conventional uses of these components in the background sections. We described the use of self-administered subcutaneous shots of insulin for daily outpatient diabetes management. We described the inpatient use intravenous insulin for patients with serious or life-threatening conditions, such as diabetic ketoacidosis or diabetic hyperosmolar coma, in the absence of RQ assessments to guide dosing. We described the special requirements for intravenous insulin including insulin dilution, concomitant potassium administration, monitoring of glucose, electrolyte, and fluid levels, and skilled nursing. We described the use of inspired and expired gas measurements in the inpatient setting on a sporadic basis for the adjustment of ventilation and parenteral nutrition parameters. We described the occasional use of respiratory gases in the outpatient setting for the determination of basal metabolic rates and in cardiopulmonary stress testing. These conventional uses were contrasted with the less conventional uses of these components in OIVIT. The differences in their frequency of use were also compared. In this decision, we are not making (a) coverage determination(s) regarding these more conventional uses. Coverage for such conventional uses may be determined by other local or national Medicare determinations and will not be considered here. The most commercially available OIVIT procedure in the U.S. involves serial infusions of insulin in a pulsed fashion. In contrast to the inpatient use of intravenous insulin administration, the therapy is adjunctive to the patient's usual diabetes management regimen. Metabolic cart measurements of inspired and expired gases, specifically respiratory quotients, (RQ), may be used for the putative assessment of the oxidative response to insulin dosing and for the determination of subsequent insulin dosing. In contrast to their uses in cardiopulmonary testing and Intensive Care Unit (ICU) management, multiple respiratory gas measurements for serial RQ assessments are often obtained on a single day. Specific criteria describing how such assessments determine subsequent insulin infusion dosing are not available in the methods sections of the published literature or the patents for OIVIT. (Aoki 1993, 1995a, 1995b, 1995c, 1999, Dailey 2000, Weinrauch 2007, 2009 a, 2009b, Aoki patent series, Gilbert patent series) The other parameters used to determine subsequent insulin dosing (possibly patient characteristics, treatment response history, and/or diagnostic test results) are not delineated in the methods sections of the published literature or the patents. Protocol measures to enhance safety during intravenous insulin administration (except for the use of *ad libitum* carbohydrates) and to systematically monitor for adverse events are not available in the methods sections of the published literature or the patents.

CMS searched for evidence regarding OIVIT, including evidence pertaining to the use of its components in the way they are utilized in OIVIT regimens. Although we focused on clinical trials, we did consider animal studies (See Background) and short-term/human physiology studies (See Evidence) because these types of studies are frequently used to establish primary efficacy, identify treatment protocol variables that impact efficacy, and identify patient or disease indication variables that impact efficacy prior to more extended clinical trials in human subjects.

Most of the animal and short-term/human physiology studies differed from therapeutic clinical studies in that the insulin dose was replacement dosing and not intermittent adjunctive dosing. Nonetheless, as in the three cited animal studies, the efficacy results in the short-term/human physiology studies were contradictory. Some studies demonstrated improved glycemic control or nutrient utilization whereas others did not. Such inconsistency suggests the presence of important variables in the regimen, technique, patient characteristics, or disease state which require identification. Thus far investigators have not been able to determine which variables, whether intrinsic or experimental, except perhaps pulse rate, glucagon level and duration of infusion, contribute to these disparate results. (Porksen 1998, Zarkovic 1999, 2000) Of note, respiratory quotients were seldom included in short-term/human physiology study protocols. As such, their role in future therapeutic clinical trial regimens was not clearly defined. (Meistas 1985)

CMS did identify nine published manuscripts for five studies in which outpatient IV insulin therapy was employed. The same proprietary treatment regimen was utilized. Only patients with diabetes were studied. Patient variables, (e.g., age, diabetes type, disease severity, and co-morbid conditions), or treatment variables, (e.g., pulse parameters, respiratory quotient response, and duration of therapy), which could impact therapeutic utility were not adequately addressed in the studies. None of the studies served as registration trials for FDA devices or drugs. No IND or IDE information was included in the methods sections.

All of these longer-term studies have significant limitations in their design, study size, completion rate, type of patient enrolled, underlying hypothesis, robustness of their endpoints, and prospective safety monitoring. Indeed, none of the studies were blinded. Only two were randomized. Most were case series. The design issues make it difficult to determine whether the investigational treatment actually results in health benefits and whether any apparent benefit is due to increases patient supervision and support, increased insulinization (which could also be achievable by more aggressive standard therapy), or the putative unique aspects of the OIVIT intervention. The design issues also limited the ability to identify and assess potentially important patient variable for efficacy and safety.

All of the studies were small (N < 100). Indeed, four manuscripts were based on populations that were subsets of larger study populations and not independent, replicate studies. Therefore, despite the number of studies, the total patient exposure in the studies was less than 250 patients. Studies of sufficient duration to establish efficacy and/or durability were: a) too small at initiation or through attrition or b) had design shortcomings. For example, analysis of only those patients who completed the studies instead of all enrollees in a standard intent-to-treat analysis can introduce selection bias. In addition, large differences in the clinical and demographic findings between the screened patient population and the entrant population limits generalizability. The small total study population size also limits assessment of benefit in patient subgroups including those from different socioeconomic strata, different ethnic/racial groups, with different diabetes types, with different degrees of disease severity and with different types of co-morbid disease.

In fact, only Type I diabetic patients were studied, limiting the generalizability of any results for OIVIT to the Medicare patient population with its preponderance of Type 2 patients. Similarly, no non-diabetic or perioperative islet cell transplant patients were studied, precluding generalizability of any evidence to putative indications in those patient populations. In addition Felber, et al. observed different carbohydrate oxidation patterns in response to a standardized glucose challenge in Type 1 versus. Type 2 diabetic patients. [Felber 1977, 1981a, 1981b, Golay 2002, Meyer 1980] This suggests that the respiratory quotient (RQ) may not have the same utility as a surrogate endpoint or for diagnostic use in guiding insulin dosage in all patient populations even if OIVIT were to be efficacious. Many of the endpoints for efficacy were subjective or poorly defined *a priori*. None were hard clinical endpoints or non-surrogate endpoints. Several studies had multiple endpoints and only reported on the variables that were statistically significant in those patients who had completed the study. The investigators did not make statistical corrections for multiple comparisons (use of multiple endpoints) and did not conduct intent-to-treat analyses on the entire study population. The researchers for one study extended the length of the study until there was statistical significance.[Dailey 2000] In another study of the effects of OIVIT on the cardiovascular factors affecting renal dysfunction, the scientists conducted the wrong statistical comparisons and also did not address baseline imbalance for mean arterial pressure (MAP), and perhaps glycemic control, that favored the OIVIT intervention arm. [Weinrauch 2007] One study used a self-report survey tool developed by the progenitor of the pulsatile insulin regimen and not otherwise used or validated by diabetes researchers. [Hammond 2004, Weinrauch 2009] The investigators further modified this survey instrument by excluding questions in which there was no discordance between the investigational and control treatment cohorts, which were the majority of the questions in the survey. Such selective alteration increases the likelihood of a obtaining a positive, but factitious statistical difference between two treatment populations, No pre-specified protocols for the assessment of safety endpoints (e.g., hypoglycemia, hypokalemia, serum lipids, and tissue lipids) with diagnostic tests were delineated in the studies despite the fact that intravenous insulin in known to have a narrow therapeutic index (safety margin) and that dyslipidemia and organ/peri-organ lipid deposition are putative risks with activation of the glucokinase pathway. There was no rigorous reporting of adverse events in the study manuscripts. The discordance between the well established risk for hypoglycemia and hypokalemia with intravenous insulin even in the highly monitored inpatient setting and the reported near absence of risk despite repeated exposures to an invasive procedure with OIVIT has not been explained by the investigators. We have no data on the total insulin dosing per session, serial glucose levels, carbohydrate consumption per session, or weight changes from *ad libitum* carbohydrate ingestion, all factors which could help explain this paradox.

There are also unanswered questions about the underlying therapeutic principles for OIVIT. The earliest reports claimed improvements in glycemic control. Putative improvements in the rate of renal function decline, antihypertensive medication reduction, and perceived disability in later studies, however, were not related to the glycemic control achieved with OIVIT. Indeed the data suggested that the mean glycemic control was equivalent or better in the control group. (Weinrauch 2007) Correlative analyses between hemoglobin $A1_c$ measurements of glycemic control or changes in glycemic control and rate of renal function decline, antihypertensive medication reduction, or perceived disability were not conducted. No rationale for this epiphenomenon of positive results in the absence of improved glycemic control was provided. It may reflect the absence of a true treatment effect and the finding of spurious positive results in the setting of statistical analyses which are uncorrected for the effects of multiple endpoints.

The function of the diagnostic tests potentially associated with OIVIT (e.g., blood/serum glucose levels, serum potassium levels, respiratory gas measurement, and urine urea nitrogen levels) has not been well delineated and validated in the published trials and patent material for OIVIT. (Aoki 1993, 1995a, 1995b, 1995c, 1999, Dailey 2000, Weinrauch 2007, 2009a, 2009b, Aoki patent series, Gilbert patent series)

Professional grade chemistry testing for potassium and glucose for the monitoring of hypokalemia and hypoglycemia respectively in OIVIT is an important element of safety. The use of home or non-professional glucose monitors is not adequate. (Diabetes Today 2009, FDA-Gaines Meter Error, FDA Glucose Meter Alerts, FDA Glucose Meter Advisory Committee Meeting 2001, FDA Meter Review Criteria, Hovorka 2006, Kost 1998, Meguro 2005, Perera 2009) The failure to have a monitoring algorithm for hypokalemia and hypoglycemia in OIVIT is problematic because of the known clinical risks.

Algorithm information for use of the respiratory quotient was absent from the methods sections of all papers. Furthermore, no head-to-head comparative studies employing OIVIT with and without RQ to establish the validity of RQ testing have been conducted. None of the published trials were structured to assess the role of the respiratory quotient either as a marker for efficacy (if any) or as a tool for any subsequent insulin dosing. Response rates, as indicated by an achievement of predetermined respiratory quotient thresholds or changes in respiratory quotient values were not presented. Correlation of respiratory quotient (RQ) values or the magnitude of change in respiratory quotient values with clinical outcomes was not presented. No studies assessed the impact of scheduled or *ad libitum* carbohydrate ingestion or antecedent meal content on respiratory quotient measurements. (Austin 2008, Benade 1973, Blundell 2002, Maffeis 2004, McGregor 1995, Root 1944, Talbott 1938) No studies included urine collections as part of their respiratory quotient determinations. None of the studies were structured to assess whether the urinary component (UUN) of RQ testing contributed to efficacy of any kind. No studies addressed the absence of steady state conditions in the presence of glycosuria (glucose loss through the urine) and albuminuria (protein loss through the urine). No studies addressed factors that could affect the reliability and predictive value of the respiratory quotients such as technique requirements, device variability and standardization issues.

CMS did not identify any high quality clinical trials for OIVIT for any clinical indication. None of the studies clearly established any efficacy attributable to OIVIT (versus increased insulin exposure via conventional treatment routes or via increased medical attention). None of the studies provided robust health outcome data of interest to the Medicare program (versus efficacy data derived from surrogate markers). (See Outcomes of Greatest Interest) None of the studies provided robust safety data of interest to the Medicare program. This would include information on hypoglycemia and hypokalemia because of the acute effects of these metabolic conditions on older beneficiaries with cardiovascular disease and other co-morbidities. None of the studies were structured or analyzed to provide robust efficacy and safety data for risk/benefit analyses in various patient populations. Indeed, the high drop-out rate in the longest and largest study raises concerns about the long-term tolerability, long-term efficacy, and long-term safety of this invasive procedure. (Dailey 2000) Furthermore, none of the studies validated the role of respiratory quotients (RQ) ± urine urea nitrogen (UUN) measurements in assessing the effect of insulin dosing and/or determining subsequent insulin doses.

Some commenters disagreed with our review or interpretation of the evidence. In response, we believe that our review was exhaustive and that our interpretation is most consistent with a fair appraisal of the evidence base.

Although OIVIT has been claimed by some stakeholders to be standard therapy for glycemic control in a variety of diabetic patient populations and for control of diabetes-related complications, the available evidence does not support this. Other Federal health programs (Department of Defense, Indian Health Service, and the Veterans' Affairs Health System) do not provide this therapeutic modality. No professional societies have included outpatient IV insulin therapy in their treatment guidelines or otherwise endorsed the therapeutic regimen.

Blue Cross/Blue Shield (California) and the Hayes Group have performed technology assessments of this therapeutic modality and concluded that the data did not support use of this treatment regimen. Many of the usual reviewers of technology, e.g., the Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, and the National Institute for Health and Clinical Excellence (NICE), have not published technology assessments on outpatient intravenous insulin or metabolic cart measurements although they have conducted other assessments of diabetes-related technology and novel therapeutic regimens. The FDA has not approved or cleared the intravenous insulin treatment regimen, and no pumps have specifically been approved for this indication. The public commenters who advocated for CMS coverage did not provide scientific data that would support their position and many had conflicts of interest.

In summary, CMS does not believe that the available data from OIVIT studies have established its clinical benefit in any patient population for any medical condition. Furthermore, the evidence of record does not demonstrate that diagnostic tests for OIVIT efficacy, e.g., respiratory quotient (RQ) testing with or without urine urea nitrogen (UUN) testing, whether as single or multiple serial tests, provide information required or useful for diabetes management.

Therefore, CMS has determined that OIVIT is not reasonable and necessary. CMS has also determined that the components of an OIVIT regimen, including its diagnostic test components and supplies, are not reasonable and necessary when furnished in the context of the OIVIT regimen. As noted previously, this decision does apply the components of OIVIT when they are used outside of the OIVIT regimen.

IX. Conclusion

1. The Centers for Medicare and Medicaid Services (CMS) has determined the following.

   The evidence does not support a conclusion that outpatient intravenous insulin therapy improves health outcomes in Medicare beneficiaries. Therefore, CMS has determined that outpatient intravenous insulin therapy is not reasonable and necessary for any indication under section 1862(a)(1)(A) of the Social Security Act. Services comprising an Outpatient Intravenous Insulin Therapy regimen are nationally noncovered under Medicare when furnished pursuant to an outpatient intravenous insulin therapy regimen.

2. Outpatient Intravenous Insulin Therapy (OIVIT) consists of an outpatient regimen of pulsatile or continuous intravenous infusion of insulin via any means, guided by the results of:
   - measurement of respiratory quotient; and/or
   - measurement of urine urea nitrogen (UUN); and/or
   - measurement of arterial, venous or capillary glucose; and/or
   - measurement of potassium concentration;

   performed in scheduled recurring intermittent episodes.

   This regimen is also sometimes termed *Cellular Activation Therapy (CAT), Chronic Intermittent Intravenous Insulin Therapy (CIIIT), Hepatic Activation Therapy (HAT), Intercellular Activation Therapy (iCAT), Metabolic Activation Therapy® (MAT®), Pulsatile Intravenous Insulin Treatment (PIVIT), Pulse Insulin Therapy (PIT)* and *Pulsatile Therapy (PT)*.

<u>Appendix A</u> <u>General Methodological Principles of Study Design</u>
(Section VI of the Decision Memorandum)

General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention’s potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study’s variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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The most pertinent chapter(s) include:

Diabetes in the Elderly. G Meneilly, D Tessier (initial draft);
Insulin Therapy in Type 1 Diabetes.A Cheng, A Hanna, T Kader, C Richardson;
Pharmacologic Management of Type 2 Diabetes.W Harper, A Hanna, V Woo, K Dawson, JF Yale, L MacCallum, M Clement, S Simpson,M Hopkins (initial draft);
In-hospital management of Diabetes.A Edwards, A Cheng, M Clement, a Hanna, R Houlden, J James (initial draft)

The CDA guideline section on intravenous insulin is delineated in the "In-hospital" chapter.
*"**Role of Intravenous Insulin Infusion**. Intravenous (IV) insulin infusion therapy should be considered during critical illness, or other illness requiring prompt glycemic control, or prolonged fasting (NPO status) (7). IV insulin infusion therapy should be administered only where frequent blood glucose (BG) monitoring and close nursing supervision are possible. Staff education is a critical component of the implementation of an IV insulin infusion protocol. IV insulin protocols should take into account the current and previous BG levels (and, therefore, the rate of change), and the patient's usual insulin dose."*

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WellPoint Medical Policy and Technology Assessment Committee (MPTAC) review of Chronic Intermittent Intravenous Insulin Therapy (CIIT), July 2008

Appendix D: Clinical Trials Listed on ClinicalTrials.gov Website

(http://clinicaltrials.gov/ct2/results?term=pulsatile+insulin; Accessed 4/19/09)

Study/PI	Subject	Diabetes	Blinding	Randomized	Control	Duration	Enrollment
NCT00228891	Neuropathy	Type 1 & 2	Investigator	No	Assigned	Not stated	Started 2005

Study/PI	Subject	Diabetes	Blinding	Randomized	Control	Duration	Enrollment
Tuller	Endpoint(s) not described	W refractory neuropathy Can be on oral rx				Q 6 mo tests 12 mo w 6 mo renewals	200 initially 500
NCT00228904 Tuller	Neuropathy via survey & NCV & quantitative sensory testing & cardiac beat-to-beat variability	Type 1 & 2 W refractory neuropathy	Investigator	No	Assigned	Not stated Q 6 mo tests	Started 2005 200 initially 400
NCT00287651 Tuller	Retinopathy via photos & Hopkins evaluation	Type 1 & 2 W PDR, NPDR, ME eye dx	Investigator	No	Assigned	Not stated Q 3-6 mo tests	Started 2005 300
NCT00539435 Tuller	Cardiac	Unspecified w cardiac dx± other complications Can be on oral rx	Open	No	Unclear	Not stated Q 6 mo tests	Started 2007 400

Study/PI	Subject	Diabetes	Blinding	Randomized	Control	Duration	Enrollment
	Cardiac QOL vs carotid US, ECHO, labs					12 mo & 6 mo renewals	
NCT00361907 Tuller	Risk Markers (Multiple)	Type 1 & 2 W complications	Investigator	No	Assigned	6 mo extended to <2 yrs	Started 2005 200 initially 500
NCT00228878 Tuller	QOL (DMIS) Not in protocol	Type 1 & 2 Can be on oral rx	Open	No	Pre-tx	Not stated	Started 2003 200 initially 500
NCT00539409 Tuller	Metabolic Integrity via QOL & lab tests	Unspecified w complications	Open	No	Pre-tx	Not stated	Started 2006

Study/PI	Subject	Diabetes	Blinding	Randomized	Control	Duration	Enrollment
	Not in protocol	Can be on oral rx				Q 6 mo tests	750
NCT00228865 Tuller	Cognitive Function	Type 1 & 2	Open	No	Pre-tx	6-12 mo w ∞ 6 mo renewals*	2003-6 Complete Not published 50
NCT00594152 Dailey	Nephropathy via renal, cardiac, neurologic, retinal tests	Type 1 W proteinuria	Open	Yes	Yes	12 mo Extended to 18 mo	1993-5 Listed 1/08 Complete Published 2000 71

Study/PI	Subject	Diabetes	Blinding	Randomized	Control	Duration	Enrollment

DMIS=Diabetes measurement Impact scale. See 2009 Weinrauch studies.
DQOL= Diabetes Quality of Life survey
Dx=disease
ME=macular edema
Mo=month
NCV=nerve conduction velocity studies
NPDR non-proliferative retinopathy
PDR=proliferative diabetic retinopathy
PI=principal investigator
Q=each
QOL=Quality of life
Rx=medication
W=with
∞=infinite or indefinite
*found only in archived protocol

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